POLIOMYELITIS VACCINE

HEARINGS

BEFORE THE

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ON

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POLIOMYELITIS VACCINE

WEDNESDAY, JUNE 22, 1955

HOUSE OF REPRESENTATIVES,
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
Washington, D. C.

The subcommittee met, pursuant to call, at 10 a. m., in room 1334, New House Office Building, Hon. J. Percy Priest (chairman of the subcommittee) presiding.

The CHAIRMAN. The committee will come to order.

Before proceeding with a panel discussion this morning, I desire to make a very brief statement. First of all, I want to express on my own behalf and on behalf of the Committee on Interstate and Foreign Commerce our very deep appreciation to the members of the panel and to Dr. John R. Paul, who has agreed to serve as chairman of the panel, to Dr. Bronk and Dr. Cornell and to all others who have assisted the committee in arranging this panel discussion this morning. We are very deeply grateful.

We are aware that each and every one of you is a very busy person with many duties and obligations. The committee feels privileged and highly honored that you have left those activities and come here this morning to assist the committee of Congress in performing its duty and discharging its responsibility.

The legislation pending before this committee at this time would authorize an appropriation to defray the cost of vaccine for those individuals between the ages of 1 and 19 who might not be in financial position to pay for it themselves.

I have felt for quite some time that there were two questions involved in the consideration of the legislation which should be considered separately and apart. One is a scientific question—a medical question. The other is a social question. In my opinion it is important that we discuss these two questions separately.

I feel that I can best discharge the responsibility imposed on this committee and on me as chairman of the committee with regard to the scientific question through a discussion such as we have planned here today with your help and your cooperation.

I believe that if properly informed the American people are able to come to wise conclusions, even admitting that among scientists, as all of us know, there are areas of controversy and difference of opinion. I as chairman of the committee, and each member of the subcommittee and the entire committee, have been asked by members of the House of Representatives countless questions on this subject. Many times we have not had the answers because we are not scientists. We have had to read newspapers and reports and talk to individuals to get the best

information we could get on the scientific aspects of the poliomyelitis vaccine and all of the related problems.

Therefore, I have felt that it was important that we have a discussion before this committee by men who are in a position to be able to discuss it with a very great degree of authority.

The ultimate purpose of the hearings, as I see it, is to create a renewed and a well-informed confidence on the part of the American people. If the results should be otherwise, then I feel that I would have failed and that the Congress would not be in a position to act wisely on whatever legislation might be reported and recommended to it.

Therefore, I have appreciated more than any of you will know your willingness to come here and help to present the true picture to us, and answer some questions in your own way. I appreciate the fact that Dr. Paul has been willing to serve as chairman of the panel. He will conduct the panel in his own way and according to the agenda that has been prepared.

May I say this: That we are seeking information. We are seeking facts.

Committee members, I am sure, unless it is for the purpose of asking a question where maybe the person speaking has not been fully understood, will refrain from asking questions until a particular theme has been finished by the panel as nearly as possible, and then if there are questions to be asked by the members of the subcommittee, there will be a time for that at that particular point.

May I state also for the benefit of those present on the panel that there are a few members of the subcommittee who may have to leave here at 10:30 for an appearance before the Rules Committee, so if they leave you will understand they are ont walking out on you but it is because of a prearranged schedule of the Rules Committee before which some of the members of this subcommittee must appear.

With this preliminary statement and again with our thanks to this panel, Dr. Paul, we are ready to proceed. At this point, if I might suggest, I believe it would be well, Dr. Paul—you probably intended to do so anyway—that you might introduce the members of the panel.

Dr. PAUL. Mr. Chairman, members of the committee, I think we recognize that this is indeed a privilege to come before your committee and indeed a grave responsibility, as chosen by Dr. Bronk of the National Academy of Sciences. I understand that in this discussion there may well be differences of opinion expressed, but that is one of the major points of the discussion. If I know some of the members of this panel as well as I think I do, there may be some slight differences expressed from time to time. But I do want to emphasize at this point that although the popular belief often is that scientists should not disagree—namely, that science is a fixed thing and if they disagree one man is right and the other is wrong—is subject to some modification. Particularly that is true in a problem of this kind when all the scientific facts are not in. It is going to have to be a question of interpretation of available data.

Now, if I can proceed to introduce the members of the panel, I will ask them to stand up if they will and we will start at the end of the table with Dr. Shannon, Associate Director of the National Institutes of Health. Dr. Francis, chairman of the department of epidemology

of the University of Michigan. Dr. Hodes, pediatrician-in-chief, of Mt. Sinai Hospital, New York City. Dr. Sabin, who is at children's hospital research foundation, University of Cincinnati. Dr. Rivers of the Rockefeller Institute. Dr. Smadel of the Army Medical Services Graduate School. Dr. Enders, chief of the Research Division of Infectious Diseases, in Boston. Dr. Salk of the school of medicine, University of Pittsburgh. Dr. Bergsma, commissioner of health of the State of New Jersey. Dr. Stanley, of the biochemistry and virus laboratory, University of California. Dr. Mayer, school of hygiene and public health, Johns-Hopkins University. Dr. Price, practitioner from Florence, S. C. Dr. MacLeod, of New York University, college of medicine. Dr. Horsfall of the Rockefeller Institute.

There are three members who were not here. Dr. Le Nevel of the Harvard School of Public Health, who had another appointment, Dr. Hammon of the University of Pittsburgh, who had to travel to Hawaii and Dr. Stokes who had to travel to France. They unfortunately cannot be here.

As Mr. Priest has indicated we have proposed in a preliminary meeting that some of us would like to present certain aspects of the poliomyelitis vaccine problem. The idea of principle back of this is that it is very difficult to answer questions on this most complex subject if they are picked out of the blue, as it were. It would seem to us that they can be best explained if they are viewed in the light of their proper perspective and background.

So with your permission, sir, we will follow an agenda which has 6 or 7 different items for discussion, in which it is our plan to have one member of our panel lead the discussion for a period presumably of not more than 10 minutes. One of my colleagues brought an alarm clock. But the point will be that we cannot possibly cover the whole subject in 10 minutes, so at the end of 10 minutes we will ask other members of the panel if they would care to comment either pro or con or in any way they wish. Then if it seems desirable to continue to discuss the subject we will do so. We hope very much that members of the committee will also ask questions. If it would seem that if a certain question is not germane to this particular topic, occasionally I might respectfully point out that this will come up later in the program.

With that, Mr. Chairman, I think we might proceed with our agenda.

The CHAIRMAN. Thank you very much, Doctor. You may proceed.

POLIOMYELITIS VACCINE PANEL: DR. JOHN R. PAUL, YALE UNIVERSITY SCHOOL OF MEDICINE, CHAIRMAN; DR. DANIEL BERGSMA, COMMISSIONER OF HEALTH, STATE OF NEW JERSEY, AND VICE PRESIDENT, ASSOCIATION OF STATE AND TERRITORIAL HEALTH OFFICERS; DR. JOHN F. ENDERS, THE CHILDREN'S HOSPITAL, BOSTON, MASS.; DR. THOMAS FRANCIS, JR., SCHOOL OF PUBLIC HEALTH, UNIVERSITY OF MICHIGAN, ANN ARBOR, MICH.; DR. HORACE L. HODES, PEDIATRICIAN IN CHIEF, MOUNT SINAI HOSPITAL, NEW YORK CITY, AND MEMBER, COMMITTEE ON THE CONTROL OF INFECTIOUS DISEASES, AMERICAN ACAD-

EMY OF PEDIATRICS; DR. FRANK L. HORSFALL, JR., ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK CITY; DR. COLIN MacLEOD, BELLEVUE MEDICAL CENTER, NEW YORK UNIVERSITY, NEW YORK CITY; DR. MANFRED M. MAYER, SCHOOL OF HYGIENE AND PUBLIC HEALTH, JOHNS HOPKINS UNIVERSITY, BALTIMORE, MD.; DR. JULIAN P. PRICE, MEMBER, BOARD OF TRUSTEES, AMERICAN MEDICAL ASSOCIATION; DR. THOMAS M. RIVERS, ROCKEFELLER INSTITUTE FOR MEDICAL RESEARCH, NEW YORK CITY; DR. ALBERT B. SABIN, THE CHILDREN'S HOSPITAL RESEARCH FOUNDATION, CINCINNATI, OHIO; DR. JONAS E. SALK, VIRUS RESEARCH LABORATORY, UNIVERSITY OF PITTSBURGH, PITTSBURGH, PA.; DR. JAMES A. SHANNON, ASSOCIATE DIRECTOR, NATIONAL INSTITUTES OF HEALTH, BETHESDA, MD.; DR. JOSEPH E. SMADEL, ARMY MEDICAL SERVICES GRADUATE SCHOOL, WALTER REED ARMY MEDICAL CENTER, WASHINGTON, D. C.; AND DR. WENDELL M. STANLEY, BIOCHEMISTRY AND VIRUS LABORATORY, UNIVERSITY OF CALIFORNIA, BERKELEY, CALIF.

Dr. PAUL. I shall call first on Dr. Sabin. I will distribute copies of the agenda for those who wish them. Dr. Sabin will discuss the problem of poliomyelitis in the United States.

PRESENTATION OF DR. ALBERT B. SABIN

Dr. SABIN. The purpose of this presentation is to give some idea of the incidence and importance and behavior of the disease for which prevention is now being sought. I did not get this assignment until late yesterday so I will not come forth with a great many charts and statistical data because I haven't got them. I did not spend last night in the laboratory.

So I am going to give you this picture as I know it, having worked in the field of poliomyelitis for 25 years now. I have a certain picture which I shall try to translate to you in simple words and I hope that the panel will not quibble about 5 percent or 10 percent more or less here or there. I have, therefore, set down a number of questions to which I shall try to bring answers. Therefore, to get to the heart of the problem immediately, I would like to ask the question, How many polio cases are being reported each year in the United States during recent years and what does it mean?

Roughly in recent years there have been reported 35,000 to 50,000 cases. You must remember that this is for a population of about 160 million, and that comes to about 25 reported cases per 100,000 population. Please bear that in mind when we come to discuss later on the meaning of an epidemic of polio. But please also bear in mind that this is an average for the entire country, for all age groups, many of whom are immune. Please also remember that in different parts of the country the rate may be as low as 2 or 3 per 100,000 and in others it may be as high as 200 or 300 per 100,000.

Please also remember that not all the reported cases are necessarily paralytic polio, because many of them are nonparalytic and doctors

without the assistance, without the laboratory have great difficulty in being sure in the absence of paralysis whether or not a case is polio.

Roughly it may be said that perhaps about half of the average of about 40,000 cases per year are paralytic. Not all of those remain paralyzed. Many of them recover. But many of them do die and many do remain paralyzed.

Please also remember another thing. That on the average for every reported case of polio during the year there are probably 100 others who become immunized probably for life without any signs or with little or no signs of sickness.

All that is important to remember.

The CHAIRMAN. Doctor, may I interrupt?

I did not get that last figure. How many cases become permanently immunized?

Dr. SABIN. Roughly, and that varies at different times and different places, for every case that develops a recognized case of paralysis there are probably on the average about 100 who become immunized with little or no signs of sickness.

The next question. Has there always been so much polio in the United States? Here we have to differentiate an important concept for you to be able to follow this. We must differentiate between polio infection and polio disease.

A person may become infected with a polio virus and not become ill. Polio disease means when he becomes sick with paralysis. Polio infection we probably always have had as much as we have now in the United States. But poliomyelitis paralysis, there definitelv was less in former years.

To give you average figures, about 30 or 40 years ago for the country at large, instead of there being 25 per 100,000 reported, there were as few as 5 to 6 per 100,000. The increase is not only because our population is increasing and because there is perhaps a little more reporting of the disease, but there is an increase in the disease itself.

What is the importance of polio relative to other diseases? The statement has been made that the publicity connected with this disease has exaggerated it out of all importance to other diseases. To be sure, many other diseases of childhood and adult life are more important than polio. But one thing I think needs to be stressed, and that is that it is not only those who become paralyzed in any 1 year that count, but the accumulation over the years that counts.

Let us say that 10,000 that remain paralyzed every year remain with us a problem, and next year you have another 10,000, and so on and so on. So that at any one time you have more than 100,000 or several hundred thousand who have suffered in the past or are now suffering from the effects of poliomyelitic paralysis.

It might be interesting to mention that among those who were rejected during the draft during World War II, 1 percent of all of those were rejected because of paralytic polio. Those are figures in the archives of the armed services.

The next question: How are different parts of the population affected? First of all the role of age. The disease is uncommon under 6 months because immunity from the mother is transmitted and stays for a period of about 4 to 6 months and also because there is evidence that much less opportunity for picking up infection exists early in life.

After that, for the country at large, the group that is most heavily attacked in point of numbers and paralysis are those that are 5 to 9 years old. Next comes the group of 1 to 4 and 10 to 14. There might be slight differences. After that you might say comes the group of 15 to 30.

It is important to stress that this is no longer a disease which we should call infantile paralysis, because the disease occurs with great frequency in young adults and, furthermore, is much more severe in those in later life than in the earlier years.

It should also be remembered the figures I have just given you are different in different parts of the country and in different economic groups. This is a large country. What applies for the South of the country does not apply for the North. What applies for low-income groups living under poor sanitary conditions does not apply for the large middle-income groups and others.

I must make these statements brief. Explanations can come later.

I mention I brought up the factor of economic status. Is there a difference? I think most of us believe now that there is. Of course, all can get polio and do. But generally paralysis is more frequent in the middle and higher income groups than in the lower income groups. It is a paradox which can be explained. Here you must remember, again, that while the lower income groups we know get much more infection and earlier in life than the higher income groups, they do not get apparently as much paralysis.

Recently, I have made a survey in my own laboratory to determine what proportion of the population in their third decade, between 21 and 30 years of age, in different economic groups have already had an experience or have been immunized from polio. I studied about 225 prisoners at a Federal reformatory who came from all parts of this country and from the lower income groups and mostly from large cities. In that group (at 21 to 30) there were only on the average about 15 percent that had no demonstrable immunity to one or another type, but 40 percent still had no immunity to one or more types.

By comparison, I made a similar study on some eighty-odd medical students at the University of Cincinnati of the same age group. They come from middle income groups. There the important fact to remember, because it has a bearing on this problem is that 57 percent of those still had no demonstratable immunity to the important type 1 polio which is the cause of most epidemics. Fifty-seven percent, about three to four times as many were not immune among this middle income group, as in the low income group.

When you take into consideration the other types, then 85 percent of those age 21 to 30 in the middle income group still had no demonstrable immunity to one or the other of the 3 types.

I submit, gentlemen, that these in the third decade are just as much in need of preventive measures as are all the others.

What are the epidemics of polio? In the first place, the source of polio virus is in human beings. Perhaps the chief offenders from that are young children. The worst time for that is the summertime when they have little clothes on them, with the chances of getting virus from the hind end, where it is most prevalent and distributing it around the mouths to the others, are greatest. There may be other sources of infection, but that is most important.

We know from studies that even when there is no epidemic at any one moment about 1 percent of young children can be shown to carry polio virus.

Not all polio viruses are bad. Studies are now in progress to show that some are very mild indeed. But apparently epidemics of poliomyelitis are predominantly caused by the type 1 polio virus. That is an important factor because occasionally it invades different communities at different times.

What we need now is a numerical definition of what is an epidemic. In the old days it was regarded that an incidence of 20 per 100,000 could be called an epidemic. In view of recent experience, it is obvious that this needs redefinition.

To summarize this, then, the problem in the United States is to prevent paralysis in young adults in whom it is most severe, as well as in children in whom it is more frequent. Furthermore, because the virus is widespread among human beings and can be imported from neighboring countries and from other areas, it is important to maintain such an immunity not only during the early years of life, but as long as possible, because one does not develop resistance to polio simply by growing older.

Dr. PAUL. Thank you, Dr. Sabin.

In accordance with our procedure now, we would like to ask all members of the panel who would care to comment on Dr. Sabin's remarks to do so.

(No response.)

Dr. PAUL. Are there any questions from members of the committee about this aspect of poliomyelitis problems?

Mr. WOLVERTON. Can we assume on behalf of the experts that silence gives consent to the statement that has just been made?

Dr. PAUL. I believe so, sir.

The CHAIRMAN. Are there any questions? Mr. Hayworth.

Mr. HAYWORTH. Can you identify a successful immunization in an individual easily?

Dr. SABIN. This will come up later, but you can measure what are known as antibodies in the blood. A person who is not immune generally has no demonstrable antibodies. If he has been immunized, that is one sign that he has been.

Mr. HESELTON. Doctor, I believe you said something to the effect that for every reported case probably 100 become permanently immunized. Not being trained as a medical person or a scientist, I am not clear as to exactly what you mean by that. Would you care to tell us a little more about it?

Dr. SABIN. We mean, sir, that they become infected with the virus, but show no signs of sickness or a very mild sickness that is not recognized. As a result of this, they are immune for at least a long time. The reason we might think it is lifelong is because of studies carried out by our chairman, Dr. Paul, and his associates.

On isolated groups in Alaska, where it is known that the virus had not been present for 30 or 40 years by the fact that those under this age have no demonstrable immunity, yet all of those who are 40 years or over still had evidence of the infection that came in there some forty-odd years ago.

Mr. DEROUNIAN. Dr. Sabin, I am particularly interested in your sources of virus in children. You mention in the summertime, because

they don't wear too many clothes, the source is from the hind part of the child. Is that because of the things they might eat that are infected, and they excrete it, and it spreads that way? Just specifically how does the virus get into the child in the first place?

Dr. SABIN. There has been controversy for a long time but I think the majority opinion at the present time is inclined to believe that the virus gets into the mouth. The richest source of it is the stools. If you are covered up there is less chance. Unless the stools can find their way to another person, they cannot transmit. So when they wear less and sweat more, the chances of having more virus—that may not be the only explanation—are greater.

We know by actual test that a smidgeon of stool—you might say that which you can hardly see on a swab—may have as much as ten to one hundred thousand infected doses of virus taken from a child that by itself may be well and yet can transmit it to somebody else.

Mr. DEROUNIAN. I think this is very important. It is not a very delicate subject, if the mothers will make sure that their smaller children are clean after they visit the toilet, they might reduce the incidence of transmission, would you not say?

Dr. SABIN. That might be a reasonable deduction.

Mr. SPRINGER. Doctor, I think I am on the right subject. I want to ask in the conduct of your experiments with the University of Cincinnati students, and with the Federal penitentiary, did you use your approach to this problem or did you use the vaccine approach?

Dr. SABIN. Sir, I don't know exactly what you mean by my approach or the vaccine approach. What I did do was to find out what nature had done for them. I measured the antibodies in their blood against all three types of virus to find out what had happened in nature, even though they had no knowledge of having had polio before. What we found is something that had been shown by others before in other places for different age groups, that is, in the third decade there are about 3 to 4 times as many in the middle income groups who still lack immunity for polio as compared to those in lower income groups.

Mr. SPRINGER. What I meant, Doctor, is this. As I understand it, your theory ultimately of solution to this problem is an oral vaccine. Is that correct?

Dr. SABIN. Sir, I would like to make it clear that I have no preconceived notions. I am gathering information. I am working on such an approach. What the answer will be I do not know at this time.

Mr. SPRINGER. In order that you are not misunderstood, and that I do get your correct approach here, it has been said in the newspapers that your approach was this one, and possibly the approach of the vaccine was not the correct approach.

Would you state for the benefit of the committee whether you believe that the vaccine is a good approach or whether the oral approach is the approach which should be fundamentally taken?

Dr. SABIN. With your permission, sir, I think that this comes later on the agenda. If you have no objection, I think perhaps the chairman would prefer to have it discussed later.

The CHAIRMAN. May I ask one question, Doctor? I thought you made a very significant statement when you said that the question of the number of paralytic cases in 1 year was not as important as the accumulation over a period of years. I think that is quite significant.

Is there any statistical information available presently as to the number of paralytic cases over any given period of years—10 or 20 years, for example? Do we have statistical information on that?

Dr. SABIN. There is statistical information. I do not have it now. It is possible that some other member of the panel may know those figures offhand. I don't know.

The CHAIRMAN. Are there any further questions on this particular subject from the committee?

Mr. ROBERTS. I have one question, Doctor. I understood you to say that the prevalence of infection seemed to be lower in the lower income group than it did in the higher income group. Do you have any opinion as to why that might be true?

Dr. SABIN. I said the reverse, Mr. Roberts. What I said was that the disease was lower but infection, particularly in early life, was higher. That is an important distinction.

As to the reasons, there may be many. The only thing we know is that in countries where the sanitary conditions are not as good as our own, where the crowding is much greater, there is much less paralytic polio than in this country. There is always everywhere some, but very much less than in this country. Apparently the opportunity to be exposed to small doses and to viruses which are not so virulent, and which are not so bad, provides an immunity which then protects against the viruses that are much worse. Also the opportunity to get it earlier in life is apparently an advantage. That may obtain to our population in the lower income groups as well as to those in Africa and Asia and other less well developed countries.

The CHAIRMAN. Any further questions?

If not, Dr. Paul, you may proceed now with your agenda.

Dr. PAUL. I think that we may have a question from one of our panel. Dr. Bergsma is the only health officer present in our group. I would like to ask if he has a comment?

Dr. BERGSMA. I would like to point out one item. The statement previously made was correct, but might be misinterpreted in my judgment. It was said that there are many individuals who acquire the infection of poliomyelitis without developing obvious evidence of the disease and such individuals so infected become immune.

I agree wholeheartedly with that statement. I would only like to point out that there are 3 different types of polio virus, and such an individual becomes immune only to the 1 type for which he has just been infected.

Dr. PAUL. Do we have any other comments from the panel about Dr. Sabin's presentation? If not, we will go on to the second item, which will be the question of approaches to the prevention of poliomyelitis by vaccination.

Dr. Joseph Smadel, of the Army Medical Service School, will present this subject.

PRESENTATION OF DR. JOSEPH SMADEL

Dr. SMADEL. Mr. Chairman, I would like to begin by reemphasizing the point that Dr. Bergsma just made. There are three kinds of poliomyelitis virus. Each of these produces a clinical disease which is the same as the other. But although the three viruses are related—distantly related as cousins—what does it mean when one begins to make

a vaccine? It means that one has to make three different vaccines. The problem is 3 times as difficult as it is in other disease of which there is only 1 immunological type of virus.

So the problem then is difficult even in the light of the past experience with making viral vaccines which incidentally goes back 150 years to the original introduction of smallpox vaccine.

The two kinds of viral vaccines that are employed are living vaccines and dead vaccines. The living vaccines are made from mild strains of the virus that cause the disease. The dead ones can be made from almost any kind of strain.

Historically, then, we have both kinds that are quite old. The smallpox vaccine is 150 years old, and is a living vaccine. Rabies vaccine made by Pasteur some 75 years ago was a killed vaccine. So whenever one approaches the problem of immunizing against a viral disease, he uses this experience which has accumulated for a long time.

There are advantages in each particular kind. When one thinks of a living vaccine made from an attenuated strain, he immediately considers the fact that not very much vaccine is required. That means that it is easier to manufacture. You don't have to do it on a large scale. It means that only one injection is necessary, and usually immunity lasts for a very long time—for years.

The reason for this is that when one puts a live mild virus into the patient to vaccinate him, one really produces a mild infection. The patient actually has the virus multiplying in him just as the inapparent infection that Dr. Sabin was talking about acts, and as a result the individual makes his own vaccine, multiplies it, and then gets an immunological response to that material which he himself made.

The immunological response is measured usually by detecting antibodies which are specific against the virus and which combine with it, and when the antibodies have combined with the virus, the virus can no longer enter cells and infect them.

The disadvantage of a live virus—there are several disadvantages—is that it is difficult to find a good mild strain which will do these things that we spoke of, and still not produce such a severe infection in the patient that he is sick. So that they are hard to find in the first place.

Then it is well to recall that these things are living agents, and they change, just as we do. So that it is often difficult to keep them at just the proper point that one would like to have them.

These advantages and disadvantages, then, of the live virus are well recognized, not only in the discussion today but in other vaccines.

The killed type of vaccine has certain advantages, namely, that one can use almost any kind of strain. The virulent strain that produces disease, if properly killed, can be used to make a vaccine.

What are its disadvantages? It takes a lot of dead virus, because the patient that you inoculate with the dead virus does not manufacture more. You have to put in all of it that you yourself have made. This means larger quantities in the first place. It means several injections, and one of the characteristics of killed virus vaccines is that the immunity does not last very long. It lasts for a while but it does not last for many years as does the live virus vaccine.

The difficulty with a killed virus vaccine is to get the process to the proper stage where one kills all of the virus and still does not destroy

the virus to the point where it will no longer produce either immunity or demonstrable antibody. When one considers all of these theoretical advantages and disadvantages, most virologists usually conclude that a good live attenuated virus vaccine is preferable to a dead one. But in each instance this matter has to be considered on the basis of current available information on that particular virus and that particular vaccine.

In the last decade in this country and elsewhere, there have been attempts to prepare poliomyelitis vaccines using both of these historical approaches—both the live vaccine and the killed. Dr. Sabin is one of those who has made major contributions in the development of the approach to the use of live viral vaccines. These results to date are encouraging, but I think that it would be well for the committee to recall that progress is much slower with the development of a live vaccine than it is with the development of a dead vaccine, because one must go very cautiously from one step to the next to be sure that the strain that one chooses as a live attenuated virus really is mild enough not to produce disease, and yet is potent enough to immunize.

So while I am most encouraged by the progress that has been made in live attenuated vaccine, I shall not at this moment discuss it any further, because that is something for the future, it seems to me.

I would like to point out one of the basic difficulties with all killed vaccines. This is inherent in the nature of the viruses themselves. Viruses will only grow in living cells. So when one wants to get multiplication of a virus in order to make vaccine—whether one kills it or not—he must have in this preparation material from the live cells which produce the virus. That is distinctively a disadvantage. It becomes a particular disadvantage in killed vaccines, because one has to use fair amounts of these things.

One of the oldest of the vaccines, rabies, has this problem in it, and it is an important problem. Rabies vaccine for many years, and until very recently, was made by growing rabies virus in brain tissue of an animal, and then the brain tissue was ground up, the virus was killed by one or another procedure, and this material was inoculated into the patient who had been bitten by a mad dog.

The brain tissue itself—and it was there in enormous amounts in comparison to the virus—is capable of immunizing man so that he can get an allergic encephalitis. Experience over many years has indicated that about one in a thousand people who are given a full course of rabies vaccine may actually develop an encephalitis which comes from the brain tissue in the vaccine itself.

This is a distinct hazard. It is always carefully weighed by the physician when he decides that he should or should not immunize against rabies.

In other vaccines, the same sort of problem has arisen. Two of the vaccines that were widely used in World War II were influenza vaccine and typhus vaccine. Rickettsia is not a virus, but is a close relative of virus. It also will grow in living cells. Those vaccines were both made in embryonated chicken eggs and in each instance they contained a considerable amount of normal chicken egg protein. Most of us worried about what would be the hazard of using a vaccine that had this much chicken protein in it, because it was possible to sensitize people so that they would be allergic to chicken, not only to other

shots of the vaccine, but they might even get allergic to chicken as a food.

Over 10 million people were immunized with both of these vaccines repeatedly, and the theoretical hazards were obviously greatly overemphasized in our minds in the beginning. There were very, very few accidents of an allergic nature from these vaccines during the war, and most of those occurred on the first injection, which to the medical people means that these individuals who had accidents were already sensitive to egg and chicken before they got their first shot.

There is an ancillary point here that I will mention now. Probably it will come up later. When one puts all this foreign protein into a human being in order to immunize against a vaccine, something always happens, even though it may not produce a bad illness. Antibodies develop. At the end of World War II, almost a third of our troops had detectable antibodies against chicken proteins. The blood from these patients would react in test tubes with protein antigens prepared from chicken embryo tissue.

As far as we can tell, that has caused no difficulty. It did not cause any then and it has caused none since. But if those individuals are reinoculated with chicken vaccines, nothing happens except that now instead of having one-third of them with detectable antibodies, about two-thirds of them have detectable antibodies for some time.

How does this relate to some of the problems that are on the agenda? The same old problems have come up again with the vaccine that we are discussing today. Only now we are talking about monkey kidney tissue instead of about chicken embryo tissue or about brain tissue. The problems that come up at this point are theoretical, just as they were at the beginning of World War II about the chicken material.

We will discuss certain of these later, I am sure, but I would only point out now that in answer to the theoretical hazards, some evidence has been accumulated in the laboratory and on the wards, and a considerable amount of experience has already been obtained in the field with 5 million people vaccinated. So perhaps our original worries were not as great as they might have been.

Before sitting down, I would like to mention gamma globulin, just for orientation. Gamma globulin is not a vaccine. Gamma globulin contains the antibody which was manufactured by somebody who was infected by polimyelitis. It is already the preformed immunological response. That is put into the individual when one injects him with gamma globulin, and these antibodies are ready to go to work immediately. They are capable of initiating protection then at once.

These preformed substances are rather short lived. They disappear in a few weeks. They do not stimulate the formation of new immune substances. Therefore, gamma globulin which is an antibody preparation, should be considered in an entirely different light from the vaccine which starts the ball rolling, and the individual then produces his own immune substances.

Dr. PAUL. Thank you, Dr. Smadel. I will call now on members of the panel who care to comment on Dr. Smadel's remarks.

Dr. FRANCIS. May I make just one comment? This is with respect to Dr. Smadel's latest remarks about gamma globulin, and about his earlier ones about the function of a vaccine. At least from the point of view of getting a measure of effect or measuring effect, they presumably have the same function, that is, the gamma globulin provides

the antibody itself. The vaccine stimulates the person to produce the antibody and in each instance the antibody is presumably the protective factor which results. I think that might be a point of additional clarification.

Dr. MAYER. I would like to comment on Dr. Smadel's remarks concerning the fact that these virsuses used in the preparation of the vaccine must be grown in living cells, and therefore contain materials derived from these living cells. In this case it is the monkey kidney cells.

This, as Dr. Smadel has pointed out, poses a theoretical problem. I believe that not all the answers that we would like to have are available on this problem. But I would merely like to point out that we do not necessarily have to accept the fact that material as injected into the human being must contain this undesirable substance or these substances. These impurities can be removed and ways and means and methods have been developed for their removal almost completely.

I would like to state the point that highly purified virus can be made at this time.

The CHAIRMAN. Before you sit down, may I ask just this one question? Did you in your later reference refer to the illustration or the example used by Dr. Smadel insofar as chicken egg protein is concerned? Was that the point of your remark?

Dr. MAYER. Yes. In this case I am referring to the monkey kidney proteins which at present constitute the great majority of the material in the vaccine.

The CHAIRMAN. Thank you, sir.

Dr. PAUL. Dr. Stanley.

PRESENTATION OF DR. WENDELL M. STANLEY

Dr. STANLEY. Mr. Chairman, the only competence I have is that of a biochemist. I know that Dr. Smadel would agree with me if I would call his attention to the fact that he said these vaccines must have material in active vaccine from living cells. I would gather, I think, that Dr. Smadel would agree with me that there are techniques for removing the material if the physician or the medical research investigator wishes to have it removed.

During the World War, as he has indicated, this was a problem in the case of influenza virus vaccines. One of the jobs we had during the war as chemists was to make an attempt to remove the chicken embryo protein. This we did in a so-called centrifuge type influenza virus vaccine.

I would gather from what Dr. Smadel has said that it probably was not necessary. But this was just one of the jobs that we did.

We have in the current program of research been developing a similar chemical technique for removing the monkey kidney protein. Again I am not competent to say whether it needs to be removed. If it does need to be removed, I think the chemist has provided a commercially feasible process by which the monkey kidney protein in large measure can be removed.

Am I correct in my assumption on this, Dr. Smadel?

Dr. SMADEL. May I answer that, Mr. Chairman?

Dr. PAUL. Please.

Dr. SMADEL. I think in attempting to simplify the scientific data, both Dr. Stanley and I have been led down alleys in which neither of us are in an entirely defensible position. When I said that it must still be there, I was speaking in general. When Dr. Stanley said that it is possible to remove it, he was speaking from the theoretical point of view. Somewhere in the middle line is where we belong.

Dr. Stanley wasted—spent, excuse me—a considerable amount of time worrying about this problem in the beginning of World War II on influenza and I similarly wasted a considerable amount of time worrying about this with typhus. In each instance we did prepare materials which were good immunizing agents, which contained much less chicken tissue than the original materials did. It so happened that the material that Dr. Stanley prepared for flu was commercially adaptable and in general was applied. The preparation that we made for typhus was much too difficult from a commercial point of view and we never used it.

My only comment when I said wasted for both of our times was that in neither instance should we have perhaps been so concerned about the small amount that was left.

When one talks about purified virus—and around this table in polite scientific conversations we often use that—I would remind you that there is a certain amount of give and take there also, because there are very few virus preparations which are pure, and it is extremely difficult to define the criteria for purity of any one preparation. The more nearly pure you get, the more difficult it is to define what is a pure substance.

So I believe that we should leave the subject with the idea that it is possible to prepare materials on an academic scale and perhaps on a commercial scale which have very much less extraneous protein than those which are sometimes used.

The question comes down in the end to experience as to how far does one have to go, because whenever one purifies, then the process becomes more difficult and more expensive.

Mr. SPRINGER. Mr. Chairman, may I ask a question at that point? If I understand what has been said between Dr. Stanley and Dr. Mayer and Dr. Smadel, that these impurities can be removed—that is Dr. Mayer's contention, am I correct?

Dr. MAYER. That is right.

Mr. SPRINGER. The intention, as I understand it now of Dr. Stanley and Dr. Smadel, the only important issue to be determined is to find out what the minimum of this should be without the necessity of entirely removing the impurity.

Dr. SMADEL. That is correct.

Mr. SPRINGER. Dr. Mayer, would you agree with that statement?

Dr. MAYER. I am not sure that I understand the statement. Could we have it again?

Dr. SMADEL. May I rephrase it for you, sir?

Mr. SPRINGER. All right.

Dr. SMADEL. Mr. Springer's question is how far or how much do you demand academic purity, or are you going to take a commercial product that you can make on a large scale with a small amount of extraneous material.

Dr. MAYER. May I answer that?

Mr. SPRINGER. Yes.

Dr. MAYER. I think the simplest way to answer it is to give you some figures on some lots of tissue culture fluids obtained from Dr. Stanley that we have examined, which contain approximately 150 micrograms of material derived from the kidney cells. They also contain approximately 0.2 of a microgram of virus. It is possible to purify this to the extent where you have only approximately 0.3 of a microgram of kidney material left. I think that is not academic purity, I think this is marvelous in my opinion material for a vaccine. So the answer is that I don't think one has to insist on 100 percent purity, but it is my feeling that one can arrive at a satisfactory state of purity very easily.

Dr. STANLEY. Mr. Chairman, I am afraid that particularly you members of the committee are going to get lost in micrograms, and if so, what Dr. Mayer has just said is that the amount of virus is of the order of magnitude—and here let us give and take tenfold—of one one-thousandth to one ten-thousandth of the amount of protein material in the present vaccine.

In other words, you have from about 1,000 times to 10,000 times more material of a protein nature there that does so far as we know no good. The virus is the important part. I agree completely with Dr. Smadel that you must accept a process which is commercially feasible and which our manufacturers can take over and use. They obviously cannot make pure virus vaccine. It is much too expensive.

Mr. SPRINGER. Mr. Chairman, may I ask just one more question that is pertinent on this point? I will ask this of Dr. Smadel in order to bring it to a head.

Are all of you gentlemen generally agreed on what the maximum of the impurity can be and still be safe?

Dr. SMADEL. I will answer that by saying that I am sure that there is no consensus about the maximum that is necessary in the final product or the maximum that can be tolerated. While the others were discussing micrograms I did some rapid calculations, and would remind you that the amount of material Dr. Mayer is talking about is still fantastically small. A gram—there are 5 grams in a teaspoonful—1 gram diluted 100,000 times is a microgram. Typhus vaccines which we used in World War II contained 10 percent chicken embryo tissue. That meant that for every cubic centimeter or for every gram of cubic centimeter of vaccine—one dose—there was a tenth of a gram of chicken material in it. Japanese encephalitis vaccine was 20 percent chicken embryo.

This is the level that begins to worry me when we get up into such enormous concentrations as that. The level that Dr. Mayer is talking about is so low that that is much beyond my worry.

Mr. SPRINGER. Under the present vaccine formula as is now in production, the amount of impurity is not material?

Dr. SMADEL. I think you must qualify any answer to that. If you are speaking of the amount of impurity in comparison to the amount of virus that is there, then it is enormous. The ratio, as Dr. Mayer gave it to you, is about right.

Dr. MAYER. About 1,000 to 1.

Dr. SMADEL. Yours is 100 to 1. The nitrogen content cannot be greater than 0.02 nitrogen. The amount which can be present and was present in the typhus vaccine and some of the encephalitis vaccines was 2.0 nitrogen. So in comparison to these others, it is minute. In

comparison to the amount of virus present, it is large. It is a difficult problem to resolve.

Dr. PAUL. I don't know how technical we should get in our discussions, but we will be just as technical as the committee would like us to be.

Mr. SPRINGER. May I say, Mr. Chairman, that I am going to let the matter rest as it seems I have developed it as far as I can, but I did not get a categorical answer here on the question of safety. I did get an answer, but I hope we can clear that point up, because it is already in the record, and it is not conclusive in my opinion, as it should be.

Dr. PAUL. Have we got the question clearly in mind for discussion?

Dr. ENDERS. I think perhaps I might try to answer what I think you have in mind, Mr. Springer, by saying that in this case, there is some concern over the protein from the kidney in the vaccine because it is possible, on theoretical grounds anyway, that this kidney protein may give rise to reactions on repeated injection in the human being so that it might eventually cause damage to the person's own kidney. I know we are not in possession of concrete information that that will take place. We have analogies, just as Dr. Smadel has mentioned, in the case of the brain protein where there is a reaction that occurs in some individuals. If it is necessary to repeat the inoculation yearly or every 2 or 3 years, it is entirely possible that certain rare individuals may develop sensitivity and damage to their kidneys.

Nobody can say whether the amount in the vaccine at present is enough to do that or not. Only experience will tell us that in man.

Mr. SPRINGER. Dr. Salk seems to have his hand up. Can he comment on that, Dr. Paul?

Dr. SALK. This is a question, of course, that came to our minds very early, principally because of the experience with central nervous tissue, that is, brain material. We explored this experimentally. We explored the question in human subjects, and we also gave some theoretical thought to it as well. I should like to give you the benefit of the facts that we have acquired in human subjects.

First I might say that it is possible to take this vaccine or this normal kidney material and inject it into animals and produce antibodies. We have tried to do this with animals and have done this repeatedly without damaging the kidneys. We have done this using an adjuvant, a potentiating substance, so as to make the kidney vaccine, if you will, even more potent than it is when used straightaway. We did not use these fantastically small quantities—I say fantastically because they are incomprehensible just as it is difficult to comprehend the distance from here to the stars—but we used heavy suspensions containing 10 percent kidney tissue so that it was a really gunkey mess when inoculated.

We were unable to produce kidney damage in animals.

What analogous experiments have been done and experiences have been had by others? It has been found by and large that when one directly inoculates an animal with kidney material, one does not do damage to the kidney of the animal inoculated. But if one were to remove the blood from the animal that was inoculated, and the blood now contains kidney antibodies, and were then to inoculate this blood into, let us say, rabbits, with an extract of kidney of a rat, nothing happens to the rabbit. But if you take the blood from the rabbit and

inoculate that blood back into the rat, that blood now has antibody against rat kidney, and you will produce a destructive effect on the rat kidney.

Our own reasoning has been that the danger that can come theoretically would be if we were to take human blood after vaccination, assuming it has enough monkey kidney antibody, and then transfuse monkeys with human blood. Then we can visualize a situation in which damage to a kidney can be done.

In our own thinking this is the extent to which the concept seems to apply. Then there are other analogous situations. For example, we have used liver extract in medicine for many, many years. We have used other organ extracts, insulin, extracts of the adrenal glands, extracts of the pituitary glands. They have been used in medicine. These are highly crude extracts, but they have been used for a number of years, and there has not been any great concern about the destructive effect of such repeated injections.

The situation with brain and skin and lens of the eye are quite different. These tissues exist outside of the body, so to speak. The animal has the capacity to produce antibody to these tissues and a destructive effect upon the same tissue. Therefore, I think we must not put the brain and the kidney into the same category, in these considerations.

We pursued this further and found that when humans are inoculated repeatedly with polio vaccine and careful studies are done on the kidney function—the kind of test that one does to see if inflammation of the kidney has developed—we were unable to demonstrate any direct inflammatory action.

Dr. PAUL. Mr. Springer, does that answer some of your questions, or would you rather have further discussion?

Mr. SPRINGER. I just want to ask this one question to see if I can get an answer from Dr. Salk.

Based on all your experience with the present vaccine, this question of purity that has been under discussion is not really material?

Dr. SALK. I don't think so. I think it is an interesting and academic question, and one might say how far does one want to gild the lily. It belongs in that department.

I think it would be nice to purify vaccine further, but not for the reasons that have been implied. I think it is awfully nice to have pure things, but let us not do it for the wrong reason. Let us not do it because we are afraid of kidney damage. The clinical evidence is against that.

Dr. PAUL. Mr. Chairman, how are we coming on time?

The CHAIRMAN. We are pretty well on time, Doctor. Perhaps we have run a little beyond the schedule. But in my own opinion, we are developing here an extremely important record, and I would not want to hasten anybody. I think the discussion that has just taken place has brought to this committee information which we will be able to relay to the House of Representatives in a way that would answer a great many questions that have arisen. So I am not inclined at all to press you. You proceed, Doctor, as you desire.

Dr. FRANCIS. May I ask Dr. Mayer if he has additional information on antibody or lack of antibody in persons inoculated with polio vaccine?

Dr. MAYER. We do. We examined the blood of 114 children inoculated by Dr. Salk.

The CHAIRMAN. May I ask if that was a recent inoculation or has that been in the field trial?

Dr. MAYER. This was prior to the field trial. We found one child which developed a detectable antibody response to the kidney material out of 114. This is where one gets into a difference of interpretation. While I agree with everything that has been said by Dr. Salk, my own feeling is that it is so easy to remove most of these kidney impurities by commercially feasible processes available now, that I think it should be done, even when we do not know definitely that there is or is not danger.

There is one other point I would like to make here. In considering the element of danger, one must evaluate in terms of the number of people involved. An experiment with 20 or 50 or even 100 animals does not furnish sufficient experience to extrapolate to 10 million or 20 million children.

The element of numbers must be considered very carefully. This is one reason why I believe our information at the moment is inadequate.

Dr. SALK. I must correct one thing that Dr. Mayer said. Of the 114 children tested, they were derived, I think, from 11 groups, or approximately that many, inoculated with different experimental vaccines. This one instance to which he refers with just detectable antibody—and whether it is significant or not is something that he will not commit himself to nor I—was inoculated with an adjuvant vaccine which consisted of a mixture of the polio vaccine as we now use it with mineral oil, which greatly potentiates the immunizing effect. You will recall I mentioned that we attempted to produce just this effect in experimental animals by mixing monkey kidney tissue and oil.

This is not the kind of preparation that is being used at the present time.

Mr. SPRINGER. Dr. Salk, would this have any effect upon future blood transfusions, that is, the situation which you have just described?

Dr. SALK. Of monkeys only.

Dr. PAUL. There seems to be a desire on the part of the panel to discuss this matter a little further.

Dr. SMADEL. I would like to bring out for the committee the fact that we have spoken so far of antibodies—kidney antibodies. This has not been broken down to the kind of antibodies that are specifically directed against kidney tissue, and those antibodies are capable of producing damage to the kidney. Those things are usually called nephrotoxic antibodies, and they belong in a very specific class.

The kind of antibody that we have been talking about so far as factual data are concerned are just antibodies in man against monkey. Just as I mentioned earlier, there were antibodies in the vaccinated troops against chicken. You must remember that there are antibodies directed against the whole animal and then very occasionally they are very specific antibodies against some tissues.

I personally don't care very much about the idea of one way or another having antibodies of monkey tissue in me. I already have them. I have been immunized with monkey material. I would not

like to have nephritoxic antibodies. Nephritoxic antibodies are things I worked on very extensively during the 1930's, and they are extremely difficult to make, and to the best of my knowledge, and after several years of very intensive work, I was never able to get an individual to make antibodies against his own kidney, nor has anyone else ever conclusively demonstrated this.

This point is the crux of the situation in a very important philosophy on the cause of nephritis. This study has been investigated from time to time intensively since 1905. It has been intensively investigated for several years during the thirties. Others have done it since. It remains for someone to show that the individual that is inoculated will get antibodies against his own kidney.

Dr. PAUL. We would like to consider going on with the agenda, if possible, with the view of getting the next item through this morning, sir.

The CHAIRMAN. Very well.

PRESENTATION OF DR. DANIEL BERGSMA

Dr. BERGSMA. Perhaps this would be helpful for orientation of the committee. The discussion we have had in the last few minutes is one clearly most theoretical in character.

A hazard, if any, has not yet been proven. I am sure that if a commercially feasible method is found to make this product even purer it will be applied. Meanwhile, may I just draw a comparison between the theoretical hazard and the fact that was presented earlier that each year we have approximately 25,000 cases of paralysis from this disease?

Dr. STANLEY. Mr. Chairman, I just want for the record once again to say because of the statement, "if a commercially feasible process is found," to indicate that a commercially feasible process has been found. It has been ready at any time that the medical profession wants to insist upon it. It has been ready for approximately a year. So that if you want to remove monkey kidney protein you can remove 90 to 95 percent of it by a commercially feasible process, which commercial houses have proved within their own production laboratories is feasible.

I take no part in the argument as to whether or not the monkey kidney protein is dangerous. As a chemist, however, I say the process is available if and when you want it.

Dr. PAUL. I think it may be likely that some of these aspects might come up in the subsequent discussion.

With regard to the next item which is going to be the subject of the poliomyelitis vaccine, which has been divided into two parts, I think perhaps we might allow Dr. Salk more than the 10 minutes to cover the subject. I will set the alarm at 20.

Dr. SALK. Thank you, Dr. Paul.

The CHAIRMAN. Before Dr. Salk proceeds, may I express on behalf of myself and the committee our appreciation for your attendance? We appreciate the attendance of all of you. Dr. Salk, we were aware that you had some rather pressing engagements, and we appreciate all the more the fact that you were able to come here today and give us the benefit of your experience and your knowledge of the subject.

PRESENTATION OF DR. JONAS E. SALK

Dr. SALK. You are very kind, Mr. Priest, and I must say I come here very willingly and very happily because I feel that this is part of our job; that is, to carry out education whether it is in the university or whether it is in the country.

It seems to me that your purpose in calling this group together to shed some light where there are areas of darkness and shadows is most helpful indeed.

I have prepared here a series of questions which I should like to give some answer to, if I can.

The first is: What is polio vaccine? I have indicated here that it is a preparation containing the 3 types of polio virus, types 1, 2, and 3, in which the virus is killed, and when injected into man produces antibody and this antibody, we believe, as you heard mentioned earlier, is the thing that carries out the immune response. That is to say, that the presence of antibody is considered to be synonymous with immunity.

How is this vaccine made? Prior to the fundamental work of Dr. Enders and his colleagues, who were able to show that polio virus could be grown in living cells in test tubes. The virus as you know has to be grown inside of a living cell, and when injected into an animal it finds the proper cell, multiplies in that cell—and usually it is in the central nervous tissues, the brain and spinal cord. With the discovery by Dr. Enders that virus could be grown in cells that themselves were grown in test tubes, one literally was able to create, as some magazine people referred to it, a virus farm. One could create a fertile field in which the virus could be grown and from which it could then be harvested.

The search for the very best tissue to provide the best field in which this virus could be grown yielded the monkey kidney. I will not go into other details at the moment, but muscle and liver and intestines and various other organs, including the lung, were examined and monkey kidney by far outstripped all others in usefulness.

In addition to the monkey kidney which is minced in fine pieces and sometimes disintegrated in other ways to provide a more efficient base for growth, a nutrient fluid is added which corresponds to the blood which circulates in your arteries and veins which brings the nutrient to these cells.

After about 7 days the cells have grown out to the full capacity within the large flask and this field is now ready for seeding. The virus is then inoculated and within 3 days—and we actually use the term "harvest" in the laboratory—the virus is ready for harvesting.

I am going to draw the analogy since we use such terms as "seeding" and "harvesting" to try to express this a little more graphically, by saying that after the 3 days when virus is harvested it means that all of the fluid in that flask is gathered together into another large container and it is then ready for separation of the wheat from the chaff, so to speak. This is done by filtration so as to remove a large part of the debris and the impurities to which Dr. Stanley referred. The separation of the wheat from the chaff is never complete but the gross tissue particles are removed so that one ends up with what appears to the naked eye to be a crystal-clear solution when, in fact, it does con-

tain these billions of minute virus particles and, as you gather, some protein that derives from the soil in which it is grown.

I have written down here that this is almost pure seed when it gets to this point.

I do want to say that of all of the vaccines in this field of work, this is perhaps one of the purest. This is then treated to make the seed impossible of sprouting again when injected into man.

How is this done? This can be done in any of a number of different ways. One can just set the preparation aside and let it age or let it die as a result of aging. One could add chemicals to hasten this process. Or one could add heat in measured amount to produce this effect.

The killing of the seed or the virus leaves it still suitable to act as nourishment for cells that make antibody. When such killed seed, or killed virus, is injected into man, this seed, or virus, finds its way into certain cells which in turn, when it takes up this protein, takes up this virus, takes up this seed, will in turn produce antibody.

It is important, of course, to be sure that all of the seed in a given batch of material is killed. That this has already been accomplished has been shown by the safe vaccination of more than 6 million children in this country and additional children in other countries of the world, making a total of approximately 7½ million.

It is also important in making a vaccine to be sure that the seed is not burned to a crisp, but I will discuss this in a moment. In making a vaccine, with respect to safety, the most important thing is to be certain that there are no seeds in this large batch, in this bushel basket, if you will, that can grow.

If you start out with approximately 100 million, then more has to be done to determine if all the seeds have been destroyed, or at least that an amount less than an amount harmful to man is present. More has to be done than can be accomplished merely by taking a scoopful from this huge pile. More has to be done, no matter how large the scoop is, unless the entire batch is spread in the field and sown. This is the sort of thing that, in fact, has been done, in that total batches have been inoculated into children.

The process that has been worked out is one in which tests are made at several intervals in the killing process to see how much virus has died after each interval of time. It appears that death occurs at a regular rate. That is to say, after each interval of time, there is a certain amount that is destroyed based upon conditions that pertain. This is true if attention is paid to all of the details that are important. This killing process occurs to a point where one can no longer detect the presence of virus in a reasonable sample.

From this point on, where one can no longer detect virus in a reasonable sample, this treatment is continued in the presence of formaldehyde for about 6 or 9 days longer when in practice it takes about 2½ days for the destruction to the point where we can no longer measure.

If a test is made at this point and if all living virus seems to have gone, as one should expect from the experimental observations that have been made repeatedly, then no virus should in fact be detectable even if one were to test 100 percent of the total batch in question.

This, in fact, has been demonstrated under laboratory conditions and has also been demonstrated in human subjects who have been inoc-

ulated with virtually every last drop of vaccine with no evidence that seeds, or virus, have sprouted that can cause disease. But there have been exceptions to this.

I might say that some manufacturers have had a perfect record of laboratory tests when made at the expected time and this has been similar to our own experience. Then there have occurred occasional positive tests which were picked up by the routine tests as done before the amended regulations. Then there have been instances of frequent positive tests in the laboratory. I might say there have also been instances where the frequent positive tests or the negative tests have occurred consistently at different times.

It is clear I think from this that a laboratory that is not batting close to 1,000 leaves much to be desired. If their misses are too frequent then they must look into their manufacturing and perhaps the raw materials and all other factors that pertain.

It is also clear that if the virus is not killed by 9 to 12 days, when in fact, it should have been killed sometimes shortly after the third day, that 2 to 3 days additional heating or treatment after 12 to 15 days cannot be expected to do much more than was not accomplished in the intervening 6- to 9-day period between the 3-day point where it should have been destroyed and the point where it was expected to be destroyed.

So we must recognize that extra heating is not the answer to the question, but the fundamentals of the process in operation in a given laboratory have to be checked and tightened if necessary.

The general outline of the procedure, as I have just described, is in fact as shown by our own pilot plant operation in which we have prepared materials in batches of about 20 quarts; and it is in fact as shown by the operation of most manufacturers.

Because in some instances positive tests are found or may be found, we want to be sure that the margin of safety in a vaccine is sufficient and now the requirement has been added that two negative tests 3 days apart must be shown. The point here is to be sure that the negative test at a given point in time is far enough away from an earlier point to indicate that the process has in fact been proceeding according to theoretical conceptions.

Because of the possibility that some accidents may occur after the material has already be en prepared in subsequent handling, tests are also made on filled containers, just as similar tests are made for bacteria and molds to be sure that no contaminant has been introduced inadvertently. For virus this should not be necessary because the viruses do not multiply independently. The viruses cannot multiply unless there are living cells. There are no living cells; therefore, while this should not be necessary, it is an extra precaution that is introduced against any unknown.

The question has also been raised because of the recent events as to whether or not it is possible that virus may have been reactivated or may have come back to life again. We have never been able to demonstrate that virus comes back to life again, so to speak, if the treatment is really carried out to the point of no return. If the treatment is carried out to the point where, in fact, death has occurred, this reactivation does not occur.

This, of course, is answered by the tests on the materials which are performed long enough after preparation. That this reactivation or

coming back to life again has not happened is also clear from a large number of batches of material that have been prepared in this country and abroad and have been fully used in size batches that approximate a million cubic centimeters.

I have tried to cover in this portion of my remarks the tests that are done to control and to establish safety with respect to the virus itself.

What other tests are also done? The tests I have just described for virus are carried out in tissue culture which is by far apparently the most sensitive means for detecting the presence of virus. In addition, tests are made for polio virus by inoculation of monkeys directly into the brain and large quantities are inoculated into muscle just as in man. But for the monkey that weights 4 to 6 pounds, 10 times the human dose is used which in relative terms is about 100 times that in relation to children.

In other tests that are done for other conceivable potential factors, animals are inoculated in general toxicity tests, general inocuity tests; and tests are also made for the culturing of bacteria or molds. Tests are done to rule out the presence of extraneous viruses that might come from the monkeys from which the material is originally prepared.

What are the other general questions of safety that have been raised? The question has been raised about the Mahoney strain. I might say the Mahoney strain was selected because it had certain desirable attributes. It grew rapidly in tissue culture. If it were not for the finding of this strain early in our work, we might not have had viruses or vaccines of suitable potency for testing quite so quickly. That strain grows rapidly in tissue culture and it could also be true in man if this virus was not killed. This characteristic it seemed to us at the outset good to try to incorporate into the vaccine since it was against viruses of this particular type that we wished to immunize. That is to say, that the strain was a clear-cut severe paraylzing strain.

Since all of the viruses, as Dr. Smadel has pointed out, should be killed, any strain that has the right immunizing properties should be satisfactory.

About a year ago we discovered the Mahoney strain was not as stable as the types 2 and 3 in the vaccine. This was due to the presence of a certain chemical called merthiolate. Immediately we set about to find a strain that would not deteriorate as rapidly as the Mahoney strain. Although the cause of the deterioration has been discovered and has been eliminated, we have in the course of searching for another strain uncovered some very interesting data that show that there are much better strains so far as antibody production is concerned.

The disease producing effect of these strains, some 30-odd, are now under investigation as well as many other studies. But in the course of these studies, orientated toward developing the most effective vaccine so far as antibody production is concerned, and by these screening investigations of a variety of strains, we hope to find the most effective ones and make substitutions as the need arises or as the indications are clear.

Another general question of safety has been raised that has to do with the presence of antibiotics in the vaccine, namely penicillin. Our own experience has been such that when we have encountered penicillin sensitive individuals known to be or said to be, we have always

done skin tests on them and then proceeded, if the skin test indicated that it would be safe, to inoculate them. These individuals have been reinoculated. We have as yet, even in persons who are known to be penicillin sensitive by virtue of the fact that they cannot tolerate injections of penicillin—in some instances the physician who could not even touch the tablets—such persons have been given the vaccine with impunity.

We might consider here whether we are not dealing with a question similar to the kidney question. Is the concentration of penicillin present of a level, or order of magnitude, that should cause one concern?

Our own experience does not indicate that. An allergist has just reported a paper in the American Journal of Public Health, in this month's issue, in which he has done rather precise studies with negative results.

Dr. Francis has some observations made in the field trial. I do not know what the final experience will be with the six-million-odd inoculated, as to the extent to which penicillin sensitivity has been a factor. I am not aware of any instances where it has caused any serious concern.

Another question that has been raised has to do with the Rh antigen. I do not want to go into an elaborate discussion of this. Many of you know that about 85 percent of individuals are Rh positive, which means that their blood contains a certain factor called Rhesus factor. That is what Rh stands for.

A woman who is Rh negative does not contain this Rhesus factor in the blood. When she becomes pregnant and the contents of the uterus contains the Rh material she develops antibody and pregnancy may prematurely be terminated.

The danger that has been suggested is that we may be inducing Rh sensitivity in Rh negative individuals by the injection of the vaccine which comes from Rhesus monkeys. This has been gone into with great care and the Rh experts have indicated that the Rh antigen that is capable of producing this effect is not a soluble antigen and would be retained with the chaff that was thrown out rather than be carried through with the wheat in the preparation of the vaccine.

Therefore, this is one opinion, plus the statement that it is difficult to produce Rh sensitization even under the best of circumstances. But more direct evidence has been obtained by Dr. Abelson and Corriell at Philadelphia, to whom we sent vaccine, commercially prepared material, and they actually conducted experiments which they will report shortly but have given me permission to mention here.

Since my time is up, I will skip any further remarks about Rh. Kidney we have discussed. Reactivation of viruses we have discussed. The tests for effectiveness, I might say quickly that the most important test is the field trial experience which Dr. Francis will refer to again. The tests for effectiveness that have had to be devised to serve as the counterpart for the safety tests for live virus had to be really the safety test for effectiveness, because it is pointless to inject a vaccine that you believe will be effective but, in fact, is not effective.

Toward this end we have developed what we refer to as reference vaccine A, which we have set up as a standard of reference against which the commercially produced materials are measured.

Dr. PAUL. Excuse me for breaking in. Would it be valuable to discuss safety in the second part?

Dr. SALK. I will be glad to discontinue.

Dr. PAUL. The points that Dr. Salk has raised are those which are so pertinent on the original agenda that was given us, and on which we have 8 or 9 items; perhaps we might concentrate now a little of our discussion to that part which concerns the manufacture and safety tests.

The CHAIRMAN. Just as you consider best, Dr. Paul. We will proceed in that manner.

Dr. PAUL. We would like to hear from any number of the panel on this point.

Dr. RIVERS. I would like Dr. Salk to finish his statement of Dr. Corriell's findings.

Dr. SALK. They did two types of experiments. The first type of experiment was that of injecting children who are Rh negative with vaccine to see if they developed Rh antibodies. They did not.

The experiments were done in adults who are Rh negative. They were given vaccine and did not develop Rh antibodies. But these same adults when injected with Rh red cells did in fact develop Rh antibody.

Therefore, that would prove that the individuals had capacity to form Rh antibodies but the vaccine did not produce this effect.

Another experiment involved the injection of human subjects who had been inoculated with Rh red cells at some time in the past. They developed Rh antibodies. The antibody disappeared, but they were hypersensitive so that a very minute amount of Rh antigen at a later time would tend to produce a very striking effect.

These individuals did not react at all when given an injection of vaccine, but when given an injection of a small amount of red cells did then in fact react, which indicated that the amount of Rh antigen that could be present was so small as not to be detectable, and their conclusions, I believe, will be merely a statement of the fact that there is no evidence that Rh antibody or sensitivity can develop after injection of vaccine as prepared.

To the latter point they reinoculated adults who got the vaccine, at a later time, and nothing further happened, and when inoculated with red cells at a later time they reacted in a primary fashion, not as if they had been previously sensitized by the vaccine.

If that is too complex, I will be glad to clarify it or someone else will, but these basically are the elements of the observation.

The CHAIRMAN. May the Chair state that the two questions with regard to Rh sensitization and penicillin have been questions that members of this committee have been asked a great deal about, and whatever may be done to get a very clear record on those two particular questions will be helpful to the committee.

Doctor, you may proceed.

Dr. PAUL. I think it would be helpful if we could have any discussion from the panel about Dr. Salk's presentation.

The CHAIRMAN. Are there questions from the committee? Mr. Springer.

Mr. SPRINGER. Dr. Salk, to clarify this for the committee, there are three types of polio. How many of those are paralytic?

Dr. SALK. Are you referring to the three virus types?

Mr. SPRINGER. That is right.

Dr. SALK. Types 1, 2, and 3?

Mr. SPRINGER. Yes, sir.

Dr. SALK. Over the years it appears that 80 percent of paralytic polio is caused by the type 1 virus, roughly 10 percent by type 2, and 10 percent by type 3. That is plus or minus a number of percent. Is that all right?

Dr. SABIN. Yes.

Dr. SALK. This has been deduced from observations made in virus isolation studies from the feces of patients paralyzed, and also retrospective observations made over a number of years in blood samples that we have studied of patients at Warm Springs, Ga., some patients paralyzed as far back as 1920.

It is interesting to see that this percentage of 8 to 1, to 1, seems to hold, for types 1, 2, and 3, respectively.

Mr. SPRINGER. Then all three types are possibilities for paralysis.

Dr. SALK. Yes, indeed.

Mr. SPRINGER. In the vaccine itself, you do it in three separate injections.

Dr. SALK. Yes. The three types are in each one.

Mr. SPRINGER. All three types are in each one of the injections.

Dr. SALK. Yes.

Mr. SPRINGER. So when you are fully vaccinated with the 3 injections, it covers all 3 of these types.

Dr. SALK. That is right.

Mr. SPRINGER. Doctor, you will admit that the safety of this program is the proof of the pudding, would you not?

Dr. SALK. Yes, sir.

Mr. SPRINGER. I want to turn, if I may, for just a minute to what has been done. I believe there were at about June 15 this year 4,843,426 vaccinations that had been made—that is, of one or more. There has been a great deal in the press about the fact that there have been some people who have gotten polio subsequent to the injections.

Dr. SALK. Yes.

Mr. SPRINGER. I want to turn, if I may, to take one company A, which supplied the largest number of vaccinations, 2,513,962. It is a fact, is it not, that even when these injections are fully made, you will in the ordinary course expect that there will be a certain number of people who will get polio anyway?

Dr. SALK. Yes.

Mr. SPRINGER. I believe the correct number based upon the estimated 5-year immediate incidence for that figure would be 57 polio cases. Is that about right, Doctor?

Dr. SALK. If you are taking that from figures you have, I will believe it.

Mr. SPRINGER. There were actually 48 cases.

Dr. SALK. Yes, sir.

Mr. SPRINGER. Is it a fact, then, that actually the number of cases which were reported were somewhat less than what you would have expected to obtain normally?

Dr. SALK. Certainly you can say "not more."

Mr. SPRINGER. To take another maker of this vaccine the second largest, 834,148 injections were supplied and given. You would have expected, as I understand it, about 6 polio cases and 9 were reported.

Dr. SALK. Yes, sir.

Mr. SPRINGER. In another case, the fourth largest one, 410,684 injections were supplied, and you would have expected 4 polio cases, and got 6.

Dr. SALK. Yes, sir.

Mr. SPRINGER. You are running in all of these instances approximately what you expected to get.

Dr. SALK. That is correct, Mr. Springer.

Mr. SPRINGER. I want to clear this up, Doctor, because there is a lot of misunderstanding in the press, that this is a 100 percent thing, and nobody will get polio once it is put in their arm. Will you tell, Doctor, why you expect an ordinary incidence of approximately 57 cases out of 2,500,000? Could you clarify why you would get 57 cases in that number of injections?

Dr. SALK. The expected incidence, 57, is based upon what is observed over the previous 5-year period in a population of this size in this particular geographic area, where vaccine was not given. There was an interval between the time of inoculation and the time when antibody begins to appear, and may be presumed to begin to do much good. During that interval of time the individuals are still fully susceptible as if they had never been inoculated.

Mr. SPRINGER. There are two things. First, he may have already had polio at the time the vaccination occurred.

Dr. SALK. That is right.

Mr. SPRINGER. Second, he may have already gotten it after the vaccination had taken place but before the antibodies went to work.

Dr. SALK. Exactly. One would expect, if one follows these observations, that the number of cases observed on a weekly basis will begin to decline, and to deviate from the expected after the period when immunity could begin to be felt or begin to be effective. So these observations that you have reported here are observations made during the early period when vaccine could not be expected to have had any effect.

Mr. SPRINGER. One further point, Doctor. It has been pointed out at various times that north of the border, Canada has been having rather a success with its vaccine program. May I ask if the vaccine produced in Canada is made by the identical process used in the United States?

Dr. SALK. Yes, it is.

Mr. SPRINGER. And is it not true that the public health officials in Canada who worked on this program worked directly with all of you people here in this country working out this program?

Dr. SALK. Yes, sir. We still are consulting with each other.

Mr. SPRINGER. And all of the companies who are now making the vaccine in this country are using the identical formula that was used by the Connaught Laboratories in Canada?

Dr. SALK. Dr. Rivers is calling my attention to some differences. I was thinking, in the basic overall. There is a difference in this respect. The virus is grown in monkey kidney cells, and the monkey kidney cells are grown in tissue culture. I indicated earlier that one can either make a fine mince of the tissue and put it in the flask, and let the cells grow, or one could disintegrate the tissue in another way.

Let me explain that, and that is the difference to which Dr. Rivers called my attention.

At the Connaught Laboratories a year ago the vaccine that was made for field trial was made in cultures in which the tissue was merely minced with scissors. More recent work has shown that it one takes the monkey kidney tissue and suspends it in a solution containing trypsin, which is an enzyme that disintegrates and dissolves the cement substance between the cells, that one will get a more efficient tissue culture. And by seeding such cultures with virus, one can produce more virus. Some companies in this country have taken that step and modified their procedure to the extent that they use that type of tissue culture rather than the other type. Whether this represents in one instance cooking on a gas stove, and in the other on an electric stove, I do not know.

Mr. SPRINGER. As far as safety of these two vaccines is concerned, the difference in manufacture is nil?

Dr. SALK. Certainly from the evidence you have just presented some of the companies represented here do prepare the vaccine by trypsinized cell technique, and others prepare it as at Connaught Laboratories by the tissue mince technique.

Mr. SPRINGER. In Canada, has the same number of expected polio cases developed there that have developed in the United States?

Dr. SALK. I don't know what the figures are. Perhaps Dr. Shannon does, or someone else, as to the number of cases that were expected. I do know this, that one case did occur a day after inoculation in a child who has a minor illness 3 or 4 days before injection. That was the only instance in 900,000 inoculations.

But Canada is north of the border and polio begins to occur there much later than it does in this country, and certainly from the seasonal point of view, they were in a far more favorable position to have gotten this kind of effect than were we any place in the United States.

Mr. SPRINGER. Actually they were inoculating in Canada at what would be considered winter temperatures in this country. Snow was on the ground.

Dr. SALK. Certainly winter or very early spring.

Mr. SPRINGER. And at the same time some of this vaccine produced that was used in this country by these five laboratories was being used in the Southern States when summertime temperatures were in effect.

Dr. SALK. That is correct.

Mr. SPRINGER. And also the polio season was underway here.

Dr. SALK. Yes. The official polio season has been underway in some of those States. In some of those areas where vaccinations were carried out they had disqualified themselves from participation in the field study last year because the season had already been underway.

Mr. SPRINGER. That is all, Mr. Chairman.

The CHAIRMAN. Dr. Salk, one question. In your statement you referred to the extra heating or extra cooking, as it is sometimes called, as not being the answer, and then you mentioned also a requirement of 2 negative tests 3 days apart.

Dr. SALK. Yes, sir.

The CHAIRMAN. May I ask, is that requirement of 2 negative tests 3 days apart a part of the new regulations for testing in the manufacturing plants?

Dr. SALK. Yes, it is, Mr. Priest.

The CHAIRMAN. On the question of the extra heating, I would like not to go into any lengthy discussion of it, but I would like a little

more detailed explanation of your opinion as to why the extra heating. I didn't quite get that from your statement because you were hurrying along to get to another subject.

Dr. SALK. I would like to try to explain this.

The CHAIRMAN. Maybe I can restate the question: Is extra heating now a requirement of the more rigid tests set up for the manufacturing process?

Dr. SALK. No, it is not. In fact, one might say that the extra heating has been recognized as not the answer and therefore it is precluded in instances where it had been applied before.

The CHAIRMAN. That answers my second question. It is not necessary to go into the extra heating. I was under the impression that originally it had been recommended as a part of the more rigid test requirements in the laboratories where the vaccine is manufactured. If it is not, we will go on from there.

Mr. DEROUNIAN. Dr. Salk, I think it is very important that we get an authoritative group of statistics on this Canadian problem, because somehow the American people have drawn very unfavorable inferences from the press that Canada is way ahead of us in the handling of vaccine production, and that we are somewhat delinquent. From what has been said today, it would appear that we are on about the same par, and I think the country ought to get some authoritative information from this panel. Maybe you can dig it up during the recess, to assure the American people that the United States is generally doing a good job.

Dr. SALK. How would you like to express it? We can do it in any number of ways.

Mr. DEROUNIAN. I think you have done it here, but if there are some statistics as to the number of cases they have had, combined with the fact that they are in a more favorable atmospheric condition at the moment, that would assure the American people that the vaccine effect is about the same in both countries.

Dr. SALK. I think it has been very unfair to the American pharmaceutical industry to have created the impression that others are doing better than our own people, because figures that Mr. Springer just quoted are perfectly adequate. The number of cubic centimeters of vaccine that have been produced here during this period of time, which is the beginning of the growth phase and development of the industry, have been very substantial. I can only say on their behalf that they have done a perfectly remarkable job.

Mr. SPRINGER. Dr. Smadel used a figure a moment ago on the vaccination for rabies. That figure I believe you said, was a calculated risk of 1 in 10,000. Is that right?

Mr. SMADEL. I said one in a thousand. Dr. Rivers by my side says 1 in 5,000. If Dr. Koprowski were here, he might say 1 in 500. But it is of that order of magnitude.

Mr. SPRINGER. And you have been using the rabies test for at least 50 years in this country?

Mr. SMADEL. Longer than that.

Mr. SPRINGER. I want to go back to Dr. Salk for a question. According to these figures, I have just made a calculation here as against 4,843,000, there have been actually reported according to my figures as of June 15, 1955, 131 cases, including 92 paralytic cases, and 39 non-

paralytic cases. In figuring that out, that comes to 1 in 40,000. If that is true, then this vaccine even using the 5,000 figure which is the maximum Dr. Smadel has set for rabies injection, is 8 times as safe as the rabies injection, if my figures are correct.

Dr. SALK. Your figures include the obvious instance where there was known incidence of polio following inoculation. What I am saying really is that if you purify your figures into two categories, as Dr. Francis did in his analysis of the field trial, then you end up with a somewhat different answer. But even if you take these very crude figures, then what you have said is a fact.

Mr. SPRINGER. Thank you.

Dr. SALK. I must say that I don't like it as it is. I think the figures in the not-too-far-distant future will show a much more satisfactory ratio.

Mr. MACDONALD. Dr. Salk, since Mr. Springer has brought in the Canadian situation, I was interested in the fact that the production of vaccine is the same in Canada, but I was wondering if the check of the safety of the vaccine was the same in Canada as it is here, or has been heretofore.

Dr. SALK. I have been in very close touch with the Connaught Laboratories, and they have followed the specifications and minimum requirements as initially set forth, and on the basis of the original documents have carried through, as has also been true for most of the companies in this country.

They have introduced—they have not introduced anything new—but you are aware of the fact that the tests are done on each batch not only at the Connaught Laboratories, but in Ottawa. The reason for this I think should be perfectly obvious. This is the first year that they have gone into this business. They essentially were testing the test, just as we were testing the test last year, when it was being done not only by the pharmaceutical company, by the National Institutes of Health, but in our laboratories. Whether they will continue this practice is another matter. But it appears a perfectly natural and reasonable thing for them to have done during their first year of experience. But if one multiplies a test a number of times, one can calculate the advantages or the disadvantages.

I tried to answer your question in two ways. One is that they have used exactly the same tests, and I am trying to amplify the testing in two laboratories to indicate what the thinking was and the analogy between that situation and the situation in this country a year ago.

Mr. MACDONALD. Am I incorrect in thinking that they triplecheck or doublecheck the vaccine whereas we, under the system that we have used so far, have been content to let the checks be done by the way of these protocols in which the vaccine itself is not actually checked, but somebody in Public Health merely checks the paper protocol to see that the checkers are checking? Isn't that the system now used in America?

Dr. SALK. You are well aware of what has been said on the subject, and that is that by and large the system used here has been one in which the protocol has been examined and then spot checks have been made.

In Canada they have done both. They have examined protocols but in addition have tested in Ottawa each sample of vaccine. I have tried to indicate to you why they have done it, because this, I believe,

is their first year in a program of this kind, just as last year was our first year in a program of this kind.

Mr. MACDONALD. You feel that the fact they have had no fatalities has nothing to do with the fact that the vaccine was doublechecked?

Dr. SALK. I don't think so.

Mr. MACDONALD. Dr. Salk, I don't know anything about this. I merely read in the papers that there have been some incidents where adults in families of children who had been inoculated had come down with polio. I was wondering (*a*) if that were true, and (*b*) if it is true, have any figures been kept of the incidence of polio in adults of inoculated children?

Dr. SALK. The fact is correct. The interpretation is then the next important thing. I believe that this is probably germane to the whole question that will be unfolded relative to the report of the Cutter experience, because I believe that it is in families where the Cutter vaccine was used that these observations have been made. From this I think you can see that there seems to have been an association of this phenomenon with the use of vaccine where children have also acquired the disease. So this seems to be limited to the use of vaccine only that you might say is unsatisfactory or improperly prepared. Whether it is improperly prepared or not, it is unsatisfactory as used.

This is not true. I was misquoted on this some weeks ago where the impression was created that children who are vaccinated are capable of transmitting the disease to adults. This is not meant to imply that children who receive proper vaccine can transmit the disease. It is clear that children who receive properly prepared vaccine do not transmit any disease to adults because they themselves do not get any disease from vaccine.

I don't want to complicate matters further, other than to say that children who are vaccinated can become carriers at a later time merely because the vaccine does not prevent infection entirely, but merely is meant to prevent paralysis.

The CHAIRMAN. We have time for about one more question. The bells have rung for a quorum call. May the Chair state at this point that it is the intention of the committee to meet again at 2 o'clock, so we will expect everybody back at that time. Mr. Hayworth has a question that we may be able to get before we have to go to the rollcall.

Mr. HAYWORTH. Mr. Chairman, I have been asked by a member of another body to get this question before the group. It seems that the school authorities in a New Jersey town have asked a group of vaccinated children to stay away from school, this in the belief that the vaccinations may have been giving polio to children or may have made them carriers of disease. Will you say, Dr. Salk, whether this is possible, probable or impossible?

Dr. SALK. Not if the children received properly prepared vaccine. It is so highly improbable that one could say it is not supposed to occur.

Mr. HAYWORTH. In other words, only in case they have been improperly vaccinated?

Dr. SALK. If they received improperly prepared vaccine. But killed virus vaccine is not supposed to contain live virus, and therefore not able to cause infection in others.

The CHAIRMAN. I am very glad you asked that question, because a number of members have asked the same question of me since noting a

news report to the effect that some children were warned to stay away from school because they had been vaccinated.

We appreciate very much the morning session, and we will reconvene at 2 o'clock to continue our discussion.

(Thereupon at 12:15 p. m., a recess was taken until 2 p. m., the same day.)

AFTER RECESS

(The hearing was resumed at 2 p. m.)

The CHAIRMAN. The committee will come to order.

When we adjourned this morning's session, committee members were asking some questions of Dr. Salk on the statement he had made. If there are no further questions by the committee, you may proceed, Dr. Paul.

Dr. PAUL. Mr. Chairman, we have decided to change the agenda very slightly in view of the fact that Dr. Salk's presentation just before lunch was concerned with safety factors in making the vaccine.

There is an item here called Production Problems, which we plan to have Dr. James Shannon of the National Institutes of Health speak about at this point. Then the discussion cannot only deal with his presentation, but with Dr. Salk's presentation.

The CHAIRMAN. I think that that is a very good change in the order.

PRESENTATION OF DR. JAMES SHANNON

Dr. SHANNON. What I will try to do very briefly is to outline some of the things that have worried the manufacturers, and that have worried us, and that actually have worried the American people.

I would like to give a little background, though, to point out that there was great concern in the industry in 1954 in their attempts to prepare poliomyelitic vaccine for the field trial, which was reported by the foundation.

There was much discussion at that time of factors of safety, and testing of vaccines and certain routines were developed that seemed to assure at least for an experimental procedure, the degree of safety that would permit the experiment to be performed. It was, as you know, a successful experiment.

Things went on then in an atmosphere, I should say, of great confidence as opposed to the spring of 1954, and this confidence was probably shared by all parties concerned. That was until a relatively short time after the beginning of mass immunization there became an association of poliomyelitis with certain individuals who had received vaccine. This precipitated an investigation and study and a review of all of the facts that were available in order to determine if possible what had caused this occurrence of poliomyelitis and how it could be prevented, if possible, in the future.

I would propose to introduce this topic to the discussion if I have your permission, Mr. Priest, by reviewing first with what the present practices are as of today in the production of poliomyelitis vaccine and then perhaps to go back over these present practices in order to discuss why each of the modifications has been introduced.

In order to do that, I have a series of charts that Dr. Scheele used some weeks ago and I think they illustrate some of the points that I

would like to make. You will recall Dr. Salk said initially that poliomyelitis vaccine is made by the inactivation of virus through exposure to formalin. Conventionally, this is done at 37 degrees. PH', which in general terms means a neutral solution.

The virus concentration falls with time. Now, it is not my purpose here to discuss the rate of fall of the virus or any formal conception of how that can be described other than to say that as time proceeds, the virus concentration is lowered from a very high level to a very low level.

During the initial stages of that inactivation, it is possible to follow it by a series of quantitative tissue culture tests that indicate the rate of decrease of virus concentration.

When one gets to about one tissue culture effective dose per milliliter, a quarter of a teaspoonful, one gets to the level where it no longer is measurable in quantitative materials, but it is detectable, and it is detectable down to a level of about here [indicating].

At this level it would be roughly somewhere in the order of magnitude of 1 to 10 tissue culture effective units per liter or per quart.

Mr. HAYWORTH. I wonder if that last statement would be repeated.

Dr. SHANNON. 1 to 10 amounts of sufficient live virus to affect a tissue culture if suitably exposed within a quart of fluid.

That would indicate roughly this level here. Above that, one obtains positive tests with suitable volumes, and below that one obtains negative tests.

In the present production procedure the material is here, at 37° body temperature, or 98° F., and one reaches the point of inability to further quantitate in roughly 3 days.

If one continues the heating for a period of 6, 9, and 12 days, one gets to the point where virus can no longer be demonstrated.

In routine production now, after once obtaining a negative result with a large volume of tissue culture fluid, one then heats an additional 3 days and retests and obtains the second negative result, and this material is then ready for pooling.

I would like to use some numbers. The chances of this test here being negative and there still being live virus there, if we describe live virus as being equal to 5 tissue culture units per quart of fluid, is roughly 1 in 10.

But when we have 2 consecutive tests with those volumes, the chances of there being live virus in that amount at the end of this period of time with 2 consecutive tests, is the multiple of these 2 probabilities or 1 in 100.

So that at this period a single strain pool is considered suitable for pooling if its concentration of live virus stands no greater chance than one in a hundred of being higher than five tissue culture effective doses per quart of fluid.

The CHAIRMAN. I don't want to interrupt your chain of thought, but just to ask one question here: Would a third negative test after a period of 3 more days add any additional safety whatsoever?

Dr. SHANNON. That would increase it to 1,000, sir. That would be taken up in a moment because this probability is not left there.

So we now have in the routine manufacturing process a fluid that the best scientific methodology can produce and describe, which stands a chance no greater than 1 in 100 of containing 5 tissue culture effective units per quart.

I might say that that is not too meaningful except in so far as it permits a precise description of the test. A very good English scientist said, "You can never prove that there is no live virus in anything. All you can do is to state the safety or the characteristics of the fluid in terms of the test applied."

This is exactly what we have done.

Now, to continue with the manufacturing process I would like to show you the second chart. I spoke of a single strain pool. That would be representative of one of these flasks. There is an inactivation process which is applied to each of the strains separately, and following these two tests which I have indicated as checks here they are then pooled. Subsequent to this pooling they are subjected to a series of other tests. These include tests for certain viruses that are hazardous to man, bacteriological contamination and the like. But in addition, a third test is done to determine the presence or absence of detectable live virus.

At this state a larger volume is utilized in the test, which in itself assures a chance of no more than 1 in 1,000 that this fluid contains more than 5 tissue culture effective units per quart. So that we reach this stage here where we are prepared now to bottle it.

With the multiple of these 3 probabilities, 1 in 10, 1 in 100, and 1 in 1,000, within the limits of tissue culture technique it may then be stated that only 1 in 100,000 samples of this vaccine will have 5 or more tissue culture units per quart.

Now, again, it is difficult to define what a tissue culture unit means or a tissue culture effective unit means in terms of paralytic poliomyelitis or in terms of infection per unit. Suffice to say, as I will bring out in a moment, that this test constitutes an increase in rigidity, and an increase in the factor of safety which to my mind is of a different order of magnitude than was characteristic of the earlier vaccines.

Now, I would like to turn for a moment to some of the problems that became apparent following the investigation or during the investigation of April 26.

It became apparent that too many of the manufacturers were obtaining positive tests at this area of the curve when live virus should not be present. Now, I have said "too many." I would like to qualify that by telling you the precise facts of the matter.

In terms of one manufacturer, the base was 2 percent, that is, 1 out of 50; in terms of another it was 5; in terms of another it was 8, and in terms of another it was 19, and in terms of the last one it was 21 percent.

So the first thing we saw was that there was a sizable percentage of positive lots at periods of time when no positive test should be demonstrable. That becomes a very practical manufacturing process.

You can say that according to the theoretical concepts, live virus should not be there. In point of fact it was there, whether because of deficiencies of conception, or deficiencies of processing. From the standpoint of the manufacturer, it is less important. He must find ways and means where this does not happen at least in such a high percentage of times. This is due in part to certain tangible things—problems having to do with stirring, with filtration, problems presumably having to do with the presence of those particles. A large number of factors can be stated. But still looking into certain manufacturers, there was fairly good evidence that this could not be ascribed to any particular cause in the hands of all. One had to assume that in the

hands of manufacturers, this solid line was the probable course of the reaction rather than which had been proposed.

Again, as I say, these would appear to be the facts, and that is what I am talking to at the moment.

It was believed in going into the manufacturing data further that the habit of taking material that was positive away out here and recooking for 2 or 3 times for 2 or 3 days, each was highly inadvisable, because as Dr. Salk has pointed out, if you have gross activity out here after a period of some 9 days, the increase of cooking for some 3 days or 30 percent increase, would not be expected to do the same as the initial 3 days had done.

In other words, these particles probably had somewhat different characteristics. Now, you go out to 15 to 18 days and of course you exaggerate it.

The first thing that was done was to limit the period of time during which this recooking process is now permitted. In general, now, recooking subsequent to 12 days at the present time is precluded until evidence to the contrary, that this is a bad practice, is available. It will continue to be precluded until that is done.

The second problem was that the tissue culture tests that we utilized did not discriminate sufficiently between a vaccine that was negative here, or a vaccine here that had live virus and a vaccine that had no live virus. To give you figures on that, there were 127 lots of trivaccine—this is after the three so-called negative single lots were mixed—that were examined for the presence of absence of live virus. Remember that by test no one of these lots had live virus at the time it was mixed.

Going through the laboratories there were 15 percent of all the trivalent strains that had demonstrable active poliomyelitis virus.

The CHAIRMAN. Was that true with respect to all of the laboratories?

Dr. SHANNON. I will give you those figures, sir.

In one laboratory it was 33 percent, in another laboratory it was 9 percent. In the other laboratory it was 23 percent. The fourth laboratory had too few to calculate a percentage, and that was eight total batches. In the last one it was 4 percent. But I would say even the last laboratory that had 4 percent positives, after a presumption of negative, is too high a percentage.

This led to a very serious inquiry into how this could happen.

Again, taking simple calculations, assuming that these live viruses were small, discrete entities distributed throughout the fluid, it becomes possible to calculate how large a sample of that fluid must one test in order to make the flat statement that there is no more than a certain amount of live virus in the total container.

Now, on the basis of those considerations, the volumes of the test were increased, so that as the result of this inquiry, the volumes of the tests have been increased in all three spots that I discussed. They have been put in at more critical points in the processing and the sum and substance of it is that we feel they have built into the total process a measure of safety that was not theretofore present.

In addition, the present technique involves the examination of random samples of the material subsequent to bottling. There can be breaks in manufacturing routine, and while it was thought initially

that these breaks where an organism or a live body that does not have the ability to multiply in the absence of a cell, are so infinitesimally small as not to require examination for, it is felt now in retrospect that this was an error and all batches now are examined that way.

When I say it was in error, by that I mean flatly that this was the best advice that the manufacturers could get, the Polio Foundation could get, and the Public Health Service could get. It was that a final container test was not indicated. We feel now that it should be added.

The CHAIRMAN. May I inquire as to how many centimeters are in the container test that is now felt desirable?

Dr. SHANNON. At the present time that is being worked out with the manufacturers. That is done as a group. It will have to be subject to the Committee, the Technical Advisory Committee on Poliomyelitis Vaccine before it is formalized.

The problem here is a difficult one. By the time the vaccine is put into a container, it has a fair variety of preservatives in it. Some of them have preservatives which are in themselves very serious deterrents to the growth of tissue cells and automatically preclude the carrying on of a valid tissue culture test.

At the present time each of the manufacturers is putting on the type of safety test which he feels his own circumstance is suited to, in terms of preservative added. I might say here whether rightly or wrongly, one is not looking for that last virus particle that could be contained in the very large volume. But he is looking for a sizable amount of virus which is there as a result of a gross manufacturing error. That is rather than a residium which is as the result of inadequate inactivization.

I would like to say only two things. One is in answer to a question raised this morning that had to do with the Canadian versus the United States experience.

I would emphasize that this is Canada's first year of testing these vaccines. In anticipation of field trial, these vaccines are tested in three laboratories—the manufacturers', Dr. Salk's, and the National Institutes of Health: It was felt in this initial year, that time would be adequate to acquire a sufficient familiarity with the techniques that one could place dependence upon the manufacturers' tests.

Now I might point out in that regard that it is the opinion of a number, and this is an opinion, sir, a number of the investigators who have considered the plant data, they would say that their experience of obtaining a fair proportion of positive results as the result of their manufacturing experience this present year, as compared to the time of preparation of field trials, is due to the fact that they are now and by their own devices developing much more sensitive tests for the detection of live virus than were available to them during the initial stages of the development. I am one who is convinced that this is the case.

The last point I would like to make is a comment on Dr. Salk's statement that unless a laboratory is batting 1,000, one should be suspicious.

Sir, I would like to say that I doubt if any laboratory will bat 1,000 in the performance of a complex job such as this.

Thank you, sir.

Dr. PAUL. Thank you, Dr. Shannon.

I think we would like to hear from the panel at this point. We have had intimations that several members wish to discuss Dr. Salk's presentation, and perhaps they could be joined together.

Dr. SALK. Dr. Paul, may I just comment, to keep things close together, to sum up Dr. Shannon's points. I do want to correct the impression about batting 1,000. It is close to 1,000 now, and how close is the question.

Now, if we reexamine table 3 in the white paper to which you referred, and also table 4, we find that laboratory A has a record of 97 lots, 21 percent of which were positive.

We find that laboratory B with 235 lots, 19 percent of which were positive. Now, I believe and I don't have all of the figures, that that represents a composite of two periods of time when manufacturer B had changed his processing a certain way. During the first period of time he had prepared 86 batches consecutively, and they were all satisfactory. During the second period of time 54 batches, 30 percent of which failed, and what happened subsequently I don't know.

In laboratory C there is a footnote which says that the laboratory C was troubled with contaminations of tissue culture during this period, and hence the 8 percent of lots shown as positive probably do not represent failure of inactivation. Therefore, it could be 8 percent or it could be zero.

As for laboratory D, where 267 lots are in question, there were, I believe, during the first 130 lots about 10 and during the second 130 but 1. There were 2 additional questionable lots that were reported, for a total of 3 in that second period, only 1 of which was positive for poliomyelitis, and another had a nonspecific degeneration, and in the third was a virus that was not polio.

I am not familiar with additional details relative to laboratory E.

On the basis of this, it would appear that laboratory A stood out differently from the others in this revised evaluation, and laboratory B had two periods of time, and it was to this that I referred in my remarks earlier. That is why I am explaining the breakdown, and the analysis of table 4 which shows that laboratory A failed in its final vaccine in 33 percent of the instances is different from the 9 percent, perhaps. In laboratory C it is 23 percent and the same footnote that is in table 3 probably applies.

I merely call your attention to these facts and perhaps another interpretation. I say this largely to point out that in the course of application it is clear that a number of problems do arise and do develop, and in the course of that experience the manufacturers learn.

But even with the "crude" tests that were available—I have crude in quotation marks—it was possible to distinguish the data for the different manufacturers in these tables.

As for the comments about the theoretical conception, I think that this is one of the things in the realm of the unknown where one could speculate at great length. The point that is of considerable importance is that we agree, the committee of which I am a member, advising on the additional or amended safety requirements—we agree that what is being done is very sound indeed, and is perhaps a very substantial contribution to preparing vaccine that would be adequate.

Dr. SHANNON. I would just like to correct the doctor on one thing. I didn't mean to go into detail on these, Jonas, but in laboratory B on single strain lots, that is not two periods. It is three periods. Unfortunately applying all of the know-how that they had in the third period, and applying all of the knowledge that they thought was causing the positive results during the second period, they ended the third period even worse than the second. They attribute it in part to the fact that during that period this is one of the laboratories that is extending time of observation of tissue culture from 2 weeks to 4 weeks, and the size of the percentage of their positive cultures came up in the third and and fourth week.

Now, unfortunately the problem of contamination can never be solved, as you will agree. For the purposes of processing a positive test is a positive test. Regardless of how it become positive. That is true. While we agree, and in our report indicate that it is likely that a portion of these because of detailed data were due to contamination. What proportion are we don't know.

The trivalent pools, regardless of how many are taken away, in terms of this explanation or that explanation or the other explanation, in terms of the tests used which are relatively insensitive, they showed a lack of ability to discriminate between a single strain pool that had no virus, in quotes, and a single strain pool that had sufficient virus to come up in the trivalent pool. This I would hold is not limited to one laboratory.

Dr. PAUL. There is only one term that worries me a bit in this discussion, that the speakers have constantly spoken of, or "cooking" this vaccine. It sounds a little like "kitchen chemistry," but I can assure you that it is a complex problem in advanced chemistry which confronts us.

I would like to call now on other members of the panel, to see if they would care to discuss the last two presentations.

Dr. SABIN. I would like to address my remarks to the question of safety involved in the production of vaccine.

In the first place, the experience gained this year in 1955 on several million inoculated children has by itself shown, as Mr. Springer has already reviewed the statistical data, that a vaccine which is not harmful can be produced in this country and can be administered without fear of producing paralysis. I think the experience in this country from the point of view of numbers is greater than that in Canada or Denmark or any of the others.

That has been demonstrated. What has gone wrong then? What has happened, and why are we having all of these hearings, and why is there so much uncertainty?

There is all of that, because of what has come to be known as the Cutter incident. That has shown that a lot of vaccine, or portions of it, which could pass the tests as were then required, could nevertheless contain enough paralyogenic paralysis-producing virus to produce paralysis in a sufficient number of those that were inoculated, that varied from 3 per 10,000 to 5 per 10,000, but a total number of almost about 60 cases of paralysis that you wouldn't have expected on the basis of occurrence.

Not only that but the evidence is now pretty clear that in those instances not only with the inoculated children themselves endangered

but members of their family were also endangered because those children after inoculation were then putting out the virus in their stools and infecting their parents, some of whom have become paralyzed and died.

The question before us, therefore, is this: What can be done to produce safe vaccine with regularity, and have the new tests Dr. Shannon has just described given us the assurance that another Cutter incident can not occur again in the future?

I know of nothing that will set back the possibility of immunizing against poliomeylitis, and I want to stress here my belief that a great advance has been made, the possibility of immunizing does exist. I know of nothing that would set it back for more years and destroy public confidence more than another Cutter incident.

Therefore, are the new tests sufficiently adequate to prevent such an incident? I must say that perhaps they are. They are certainly better than the previous ones. But can we be sure that they will prevent it? My own answer is that I cannot say for sure that they will, because it has not yet been shown that if these tests were applied to the lots that have already given us trouble in the field, that they would have been picked up.

Now why is there all of this talk of a danger about a little bit of virus that skips out and gets away from you? The only reason for that is because there is now in this vaccine at least one virus, the important one, type 1, Mahoney virus, which is the more virulent, that is known, and the smallest amount of it that gets away can produce paralysis.

Therefore, it has been the feeling of many people that I know around this table, and other virologists in the country, that the best thing that could be done to insure safety and avoid further trouble is to replace as soon as possible this particular virus, perhaps the other two types are not as virulent, but other viruses which are potentially less dangerous, and which by tests in monkeys show can be administered in 10 million times that amount and yet not produce paralysis in a monkey.

One infected dose of the Mahoney virus injected into the muscles of a monkey can produce paralysis. Ten million of the others injected into the muscles of monkeys will not produce paralysis.

Now, several years ago when the program was started there were no such strains available. It was a nice hope, but there weren't any. But developments in the last 2 years have given us such strains. We ourselves have isolated them from healthy children in this country, and have produced them in our own laboratory experimentally, so that now there are available for each of the three types of polio strains which do not have the potential danger of the ones now used.

Therefore, I think it is my recommendation, which I made at the last annual meeting of American Medical Association, that immediate steps be taken to determine whether or not these strains which may be regarded as being so much safer will produce the same degree of immunity.

There are tests available which can be quickly carried out in the laboratory, so that you don't have to go out and inoculate thousands of children to find that out. It can be done in the laboratory by tests on animals.

Tests developed both by Dr. Salk here and by Dr. Gard in Sweden which have been correlated with the behavior of children, show that

those can be done. In accord with this, not only have several countries in Europe begun to test those strains for replacement, but Ely Lilly & Co. in this country has already obtained these strains from my laboratory, and are going ahead full speed on a pilot plant model scale to determine to what extent such replacement can be made.

Now, what does that mean in practice? Practically this poses a very difficult problem for us. In private discussions with Dr. Salk, it has almost a Solomon-like decision. What is this decision?

Dr. SALK. It was not a very private discussion then.

Dr. SABIN. We had the Chairman with us. The Solomon-like decision is this: I am fully aware of the excellent humanitarian motives of those people who do not want to wait until the best possible vaccine has been developed to provide this protection to those who may get it now. Their motives are of the best and highest. They want to give protection to as many as possible right away.

But in attempting to do it at a time when we cannot be absolutely certain of avoiding another incident such as has occurred, we may eventually do more harm than good by going too fast. For that reason, the decision that I have reached for myself—and I cannot impose that on anyone else, but I merely want to give my own thinking—is that it would be much better as of now, for the manufacturing companies to stop further production of the current vaccine with the dangerous strains, and immediately get to work, as some of them are doing already, to see whether or not they can produce antigenically equally as good vaccine with the other strains which are now available.

That is, so that by the end of the year a good program might be started, all of the inoculations could be given at a time of the year when there is little polio in the community, and the three inoculations which Dr. Salk proposes could be completed before the next season, and the vaccine which is still on trial would get its best possible chance to show what it can do next year.

Ultimately, by avoiding public suspicion and the possibility of another accident, we may do more good in getting more children immunized in the end than we would by trying to do the best we possibly can now.

Dr. PAUL. Would any other members of the panel like to carry this discussion forward in any direction they care to?

Dr. MAYER. I would like to add a point to Dr. Sabin's statement which, although a theoretical point, I think has an important practical bearing.

We have shown you, or Dr. Shannon has shown you, the curves of inactivation of the virus and, Dr. Shannon pointed out, you get into a zone where you can no longer measure. The virus is cooked for a period of time longer in order to provide a safety margin.

I think it should be very clear that since you cannot measure, this is an assumption. This assumption might be erroneous. I am not saying that it is, but what I do want to point out is that we have available from Dr. Stanley's laboratory highly purified virus which can be tested in high concentration, meaning that in tissue culture or in animals, a much higher concentration or much larger amount of material can be tested than will ever go into a human being. Thus, a real known safety factor of 1,000 or even 10,000 can be introduced, rather than an assumed safety factor as at present.

Dr. HORSFALL. I would like to make one or two comments which are merely additions to what Dr. Sabin has already presented before the committee, and merely to make certain that there is no idea that Dr. Sabin was suggesting that the viruses he proposes be tested in a vaccine should be used without inactivation.

I am quite sure that his intent was that it should be understood by all here that he proposes that relatively a virulent strain be substituted for those now used, but that they also be completely inactivated.

Is that correct?

Dr. SABIN. That is correct.

Dr. PAUL. Dr. Stanley?

Dr. STANLEY. It might be well for a chemist to give at least a chemical theoretical explanation of this borderline area.

I suspect you, as laymen, may be wondering about this shadow-line zone between safety and danger. Eventually what is taking place here is a chemical reaction, a combination between formaldehyde and poliomyelitis virus in a medium in which the virus makes up one part per thousand of the protein. Formaldehyde reacts with all of the protein, and not only the virus nuclear protein.

This reaction is a chemical reaction. It has what we call an equilibrium constant, and it may have a series of such equilibrium constants. The chemist will tell you that in such a reaction it is theoretically impossible to end up with a situation in which you have no active virus. This is a theoretical consideration.

This curve which has been shown is one which will bend. On that basis alone, the manufacturers' data indicate that they find that to be the case in truth.

From a biological standpoint, there is also the possibility of viruses of differing resistances. If you have a virus which is very resistant to an inactivating agent, you may have this survive. This will give you the same type of a curve which goes up.

From this chemical and this biological standpoint, then, you have this no man's land where it is difficult to determine whether or not the virus is active and will cause disease, or has been inactivated and will not cause disease.

But from a chemical standpoint, it is even worse than that. We found years ago, working with a plant virus, that it is possible to treat it with formaldehyde so that it is inactivated by all tests which can be applied. You can put it away and leave it on your shelf for months and test it from time to time, and it is inactive. By the simple chemical treatment known as dialysis, it is possible to get activity back again and to reactivate the material.

This complicates situations, because you could take something which is completely inactive by all tests, and subject it to a chemical treatment, which might conceivably take place by injecting it into human cells, and get dialysis and get reactivation.

So this is a very tricky business. It is one which requires much study and much data. For that reason, I think the chemists have been worried about the nature of this inactivation.

Many chemists are seeking better inactivating agents. They are seeking other procedures, such as the use of ultraviolet light. Recent information indicating that the poliomyelitis virus has 30 percent nucleic acid in it would make it seem probable that treatment with ultraviolet light might be a preferable method of inactivation.

These are some chemical considerations which I have tried to explain in relatively simple terms to indicate some of the chemical reasons why the manufacturers in this process come up with 4, 23, 9, 33 percent positive cases in material which should under normal conditions, according to other theoretical considerations, be inactive.

The CHAIRMAN. Dr. Stanley, may I interrupt you just briefly to ask this question: You stated once or twice this morning that there was a process available which had been available for a year which would purify the vaccine. I believe that was insofar as removal of any kidney elements were concerned.

Dr. STANLEY. Removal of a major portion of it.

The CHAIRMAN. Would that same process apply to the inactivation process of manufacture?

Dr. STANLEY. No.

The CHAIRMAN. In your opinion as a chemist, is there a process which would clearly do that?

Dr. STANLEY. The purification process has nothing to do with the inactivation process.

The CHAIRMAN. I wanted to separate it, because I thought there might be some confusion.

Dr. STANLEY. The two are completely separate.

Dr. SALK. I was a chemist once, and so I shall not talk as a physician for a moment, and discuss my experiences with formaldehyde as a chemist.

There are lots of things which one does not know about reaction of virus, proteins and formaldehyde, and there are a lot of things we do know. We do know that the combination of formaldehyde and the virus at certain groupings on the molecule is a reversible one. We know that other combinations result in what we refer to as irreversible complexes, that eventually go on to death.

That is what I meant before when I said "treatment to a point of no return."

This latter process does not occur precipitously and abruptly, as occurs with, let us say, the combination of the formaldehyde with the amino groups on a molecule, but in the "killing" process, these take place over a period of time.

This kind of reaction which results and which is a very complex one is linked to the question of life or death. It is not the same kind of simple chemical reaction Dr. Stanley referred to in all instances.

The use of dialysis to demonstrate reactivation is actually part of the safety-testing procedure. It is something which I remember discussing with Dr. Stanley when we raised this question about his experience with the plant virus, which I think was treated and was clearly in the twilight zone, where I think one would question seriously whether or not treatment had been carried out beyond the point of no return into this particular margin we talked about as the margin of safety.

As for methods of inactivation, I think you see clearly there are more ways of killing a cat than by choking it with milk. One can do this in any of a number of ways. But, however you do it, it must be done with a clear understanding of all of the factors involved.

I make no plea for anything. I have nothing to sell, neither ideas nor vaccine. I merely want to call attention to the fact that in the

hands of some manufacturers, the experience was 2 percent failures, and in others 21 percent.

Is this indicative of an intrinsic law of nature that applies, or could this perhaps be the method of handling?

I think it is also clear from our conversations with the manufacturers in recent weeks that they did not make the necessary effort to attempt to establish whether or not this straight line which we have been talking about, this curved line, is or is not. I notice the line has gotten a little straighter down to the point where it can be measured. This has been our own experience.

We have attempted to measure it below the line, so to speak, by such experiments as taking a liter of fluid, 1,000 cc., and introducing it into individual tubes and taking these samples, very close to the point of interception of the base line. But we still end up with a zone where you can no longer make any measurements.

But on the assumption that the process is proceeding in the manner in which it is, in the visible range, it is not unreasonable to expect that this process will continue. The existence of resistant particles or nonresistant particles, these are all explanations which are offered to explain the Cutter incident.

I suppose it would not be unfair to say that if we knew what happened at Cutter, we might perhaps not be debating or deliberating or discussing this realm of the unknown. If, for example, we knew with some degree of assurance and certainty that this was a clear-cut accident of some kind which occurred after the vaccine had been satisfactorily manufactured, it would give us one way to resolve the present problem.

If, on the other hand, it was another kind of explanation that is afforded, it poses still other problems.

I think we must stick to the facts so far as we possibly can in all of these considerations. The suggestion has been made that we cannot tell, and we do not know. Well, there are lots of things that we cannot tell about, and lots we do not know, but there is a great deal we do know.

We do know that it is possible to make vaccine and to inject every last cubic centimeter into children, which represents a total batch, and we know what the results have been under those circumstances.

I say these things merely to counter some of the theoretical discustion, which is all very interesting and very nice, but let us not lose sight of the forest for the trees in all of these considerations.

Dr. PAUL. Dr. Rivers?

Dr. RIVERS. Mr. Priest, Dr. Sabin has admitted that a safe vaccine can be made. Right after that he suggests that we stop making a safe vaccine and make a safer one.

I should like to differ with him, and I should like to make a plea at this time that we do not stop making the safe vaccine.

I do not know what safer is than safe. He himself admitted that it was a safe vaccine. For that reason I have no argument with him about the matter.

I would suggest that we continue to make a safe vaccine and not stop. I think it would be tragic if we stopped.

Now about the use of formaldehyde in the inactivation of vaccines, perhaps Dr. Stanley does not know, but formaldehyde has been used

many, many years for the inactivation of viruses other than this virus, and it has been used for the inactivation of bacteria.

As a matter of fact, we have had more experience in the use of formaldehyde in the inactivation of substances for vaccines than we have on any other substance.

We have had experience with chloroform, and we have had experience with phenolic acid, but most of the vaccines which have been used, both bacterial and virile, are inactivated by formalin.

It seems to be the best agent. It does inactivate and it has the peculiar quality that some of the other substances do not have, of not destroying the thing we want, and that is the potentiality of the substance we want to immunize.

Many things will kill or destroy or inactivate viruses, but at the same time the products are no good as vaccines because they will not immunize you.

So formalin is an old friend among the vaccine makers and, so far as I know, it is the best substance yet found. If some good chemist like Dr. Stanley finds a better one, I am sure all biologists and manufacturers will be happy to use that better substance, Dr. Stanley.

Dr. PAUL. Mr. Priest, I wonder if we might turn the conversation back to the committee for a moment. We have a number of complicated problems that we have given. I certainly am going to bring it back to the panel again momentarily, but we would like very much to know if they would care to ask us questions at this point.

The CHAIRMAN. Thank you very much.

Dr. SABIN. I think I have been misunderstood by Dr. Rivers, and I want to make myself clear.

The CHAIRMAN. You are recognized for that purpose.

Dr. SABIN. I know Dr. Rivers is the first man from whom I learned about viruses, and therefore I make my statement with trepidation. But he heard part of my statement correctly when he said that I myself have indicated that safe vaccine can be made. But he has one ear in which he does not hear too well, and I think that is the one. I added to that, "but our difficulty now is that we do not know when we can make it with regularity."

It is for that reason that I proposed that changes be made.

Dr. Rivers also knows that some vaccines can be made safe, and others not. Dr. Smadel here has had an experience in making a vaccine against Venezuelan encephalitis with formalin, and it passed the animal tests. But when inoculated in human beings, it produced disease.

The CHAIRMAN. Thank you very much.

I have only one question at this point. Dr. Shannon, I gathered, not from any one particular thing you said but from the substance of your overall statement, that it might be the intention of the Public Health Service to make even more rigid the tests or the minimum requirements than are now in effect, and which superseded the minimum requirements put into effect on April 12.

Did I properly interpret your statement that that is a possibility?

Dr. SHANNON. The April 12 requirements have already been modified.

The CHAIRMAN. I am aware of that.

Dr. SHANNON. At the present time, there is a committee designated as the technical committee on poliomyelitis that has a number of things

under very active consideration, which will be applied to the manufacture of virus vaccine at such period of time as sufficient information will permit.

For instance, Dr. Stanley and Dr. Mayer suggested that it would be highly desirable to concentrate virus so that it could be tested in small bulk, but represent a very large amount of injectible material. This is an example of one of the things which is under current study at the present time.

There is another example, that 1 manufacturer has demonstrated that a 4-week test will show certain things which a 2-week test will not. This is under study in a number of laboratories, and if it can be shown that this is in fact true, then this will be required of all manufacturers.

The final container test is under study in a number of places. At such a period of time as we have the information which says which is the more rigid or the most rigid, then this will be applied.

I think the committee should appreciate that this is really a very young vaccine. This is a very young manufacturing process. The type of vaccine which will be available a year from now or 2 years from now or 3 years from now, will have the type of refinements which only time can permit. What they are, at this time, sir, I do not know.

The CHAIRMAN. It is fair to say that the question of minimum requirements is a continuing study, and that they may be modified from time to time as experience and study would indicate to be advisable?

Dr. SHANNON. That is right.

The CHAIRMAN. Mr. Wolverton?

Mr. WOLVERTON. Dr. Sabin, I would like to ask a question with reference to your statement a few moments ago in which you indicated a course which you described as being much better. I would appreciate it if you would again express what you thought would be much better.

I am fearful that I might not do it as accurately as I should, and I do not want to be accused of only hearing through one ear.

Dr. SABIN. I must, to begin with, apologize to Dr. Rivers. I was not being facetious.

Dr. RIVERS. I hear too much with the other one, however.

Dr. SABIN. My point was that if we have another Cutter incident, the difficulties of loss of public confidence in the vaccine, which was very high to begin with, and the difficulties which we have now, would become magnified. Therefore, if such a vaccine were used this summer, and we had another similar incident, it might set back the whole program of vaccination for a very long time.

There is another consideration. We know that when vaccine will be used this summer, cases of polio will be occurring regardless of the vaccine, and the vaccine will have nothing to do with it. But in view of what has happened, we are all going to have a terrible time to explain to doctors and to parents that the cases, thousands of cases of polio which we must expect to occur in the next few months, are not due to the vaccine, which takes time to immunize, but that they would have occurred anyway.

So that whatever we do this summer, we would be in trouble. It would not be the best test for the vaccine.

Because I want to see the best possible conditions for a good thing to receive its trial, and to regain public confidence, I said that I think

it would be better in the end if it were postponed until this fall, with vaccine which does not have the potential dangers which we cannot predict now.

Mr. WOLVERTON. I can very readily assume that you have come to that conclusion after considerable thought. Did you have that viewpoint before the Cutter incident?

Dr. SABIN. Sir, I have that viewpoint because of personal information that I have on tests which are admittedly still incomplete on Cutter material, which indicates that material which has been responsible for the production of paralysis in children has yielded negative results in tissue culture tests.

Therefore, it would appear that human beings are at least as sensitive as a tissue culture bottle, and since we inoculate 1 million human beings, and we cannot possibly inoculate even 100,000 or 10,000 tissue culture bottles, we will always have that potential danger as long as these dangerous strains are contained in the vaccine.

If we can substitute for that strains which, even if a little bit is left behind, will not constitute such a danger, I feel we will be on much safer ground.

Dr. SALK. I should like to hear an answer to Mr. Wolverton's question, too.

Mr. WOLVERTON. Would it be appropriate for me to ask, or is it of too personal a character to inquire whether you expressed the opinion which you have just stated, previous to the use of the vaccine which resulted in the Cutter incident?

Dr. SABIN. If you mean, have I expressed the opinion that no vaccine should be made with the Mahoney virus in it, then at a meeting of the American Medical Association in 1953, I presented a paper which has since been published in the American Journal of Diseases of Children, in which I stated the opinion which was shared not only by me but by many colleagues, that the Mahoney virus is a potentially dangerous virus for one reason or another. If it contaminates a vaccine, it could be the cause of a great deal of difficulty, and that therefore no vaccine should be made with this dangerous virus in it.

Mr. WOLVERTON. Did you have any opportunity to express this same opinion that you have today, previous to the use of the vaccine?

Dr. SABIN. You mean in 1955? I expressed it in 1953.

Mr. WOLVERTON. But I am asking as of now—immediately preceding the use of the vaccine—whether you suggested at that time that the use of it be withheld until next January instead of proceeding with it during 1955.

Dr. SABIN. No. That view I have expressed for the first time here.

Mr. WOLVERTON. This may be inappropriate for me to ask, but I do not know of any other way to get information than to ask. If you do not want to answer it for any particular reason, that is all right. Do you know whether any members of the panel who are present today agree with your statement in that respect, and would it be appropriate for me to ask whether they do agree with it or disagree with it?

Dr. SABIN. As for the members of the panel who are here present, I think it would be best if you would ask them.

There was one member of the panel who could not attend, Dr. Hammon, who presented or sent a memorandum, which he has submitted before, in which he has requested or suggested or made the same

recommendation. I have this memorandum from Dr. Hammon here, and I can place it in the record if you so direct me.

(The information referred to follows:)

SUPPLEMENTARY RECOMMENDATION, W. McD. HAMMON

We agree that the suggested changes for the interim and the future are reasonable measures toward increasing the margin of safety of the product. However, it is not felt that this is necessarily adequate to prevent another incident like that which occurred with certain batches of the Cutter product. Therefore, I feel that I should go one step further than the recommendations of the other members of the committee and recommend temporary discontinuance of releasing vaccine.

Further quantitative and comparative testing on the incriminated Cutter lots and filling sublots and more complete and accurate epidemiologic data regarding attack rates in the different bottling lots can be expected to clarify the situation further. Furthermore, one or more lots of vaccine from another manufacturer is suspect from available epidemiologic data, and further laboratory study on these lots is indicated. All further release of vaccine should be stopped until these data are available and until specific measures can be considered to prevent any subsequent outbreak of cases due to an excessive amount of live virus. Removal of the Mahoney strain from the vaccine is the most important single change which could be made at present. Also, it is apparent that most of the manufacturers are without a suitable, consistently reproducible procedure at present. Much experimental work for improvement is underway and many more matters for investigation are under consideration by them. Under the pressure of current production they are unable to devote adequate time, personnel and equipment for these studies. The immediate adoption of the suggested changes will not greatly reduce the known difficulties under which several are working but may even multiply them due to increased total sampling and testing. More time is needed for these and various other reasons before a vaccine of adequate safety can be consistently produced in large quantities by most of these firms.

Until further study of production and laboratory methods and of epidemiologic data has been made, it is our opinion that no more vaccine should be released for distribution. It is estimated that with good fortune, a vaccine that would be considered as having an adequate margin of safety might be available in about 6 months.

Mr. WOLVERTON. I have been impressed with the manner in which you have stated that it can result in more harm than good by a too early use of the vaccine. I think we have had some degree of experience in that respect.

As you have previously stated, it has created some uncertainty on the part of the people which might have been avoided if there had been a delay to a later date or a different season of the year.

That has impressed me as having a great deal of merit to it, and it is for that reason that I am inquiring whether we proceeded with it too soon, in the opinion of others than yourself.

I think that is one of the important things we should know, because at the present time the vaccine is being used in some communities and it is being used at a time when poliomyelitis is more or less the expected thing.

For that reason, I think it is a very important question, and it is important for us to have the benefit of such a distinguished group as is gathered here today as to whether we should wait until next January or whether it is the thing to do to proceed immediately, in the hope that it will be beneficial.

Have we any way of ascertaining what the panel thinks about that?

Dr. PAUL. I think that we can call on members to discuss this point.

Dr. HODES. Could we postpone that to the end of the discussion? I think other things should come up ahead of that.

Dr. PAUL. I think we had better go ahead with it at the moment.

Dr. STANLEY. This will not be an answer, Mr. Wolverton, to your question. I think that this is something that enters into the consideration. I obviously am incompetent to determine whether or not they should go ahead or should not go ahead. But there was one area which I think you ought to be familiar with. This is the first time in history, so far as I know, when a scientific program has gone ahead pretty much on the basis of not completely unpublished work, but work which is not readily available to scientists generally. Scientists over the years have followed a procedure of experimentation, checking and double-checking within their own laboratory, and publication so that the scientific world is then able to judge the results, and checking, and rechecking in laboratories throughout the world, and then decisions having been made upon that.

Now, there are very good arguments from a humanitarian standpoint which the National Foundation has followed. To speed up the normal progress of science they have operated through distinguished committees, individuals whom we would all respect for their scientific judgments. They have made decisions which in general we must respect. But these decisions have not been subjected to the criticism of scientists throughout the world. Therein we have here a special and unusual situation which I believe to be rather unique in science. It is causing a little bit of difficulty, as is obvious from the hearings here today.

I am speaking now only as a scientist would hope that in the future that scientific accomplishment and discoveries would be published and made available to all throughout the world for checking and double-checking, and then everybody on the basis of common knowledge could go ahead and in that way a program of action could be subjected not only to the thoughts and the brains of a very competent group, but to individuals outside that group.

Very frequently competency resides in some other area of the world.

Have I made myself clear?

Mr. WOLVERTON. Yes, and it leads me to ask a further question.

In view of the fact that you have used the word "unique" experience, what was, if any, the history with respect to the introduction of other vaccines when originally introduced for us? Did they have any such reaction as this, or was there a more "careful"—or probably I should not use that word.

Dr. STANLEY. I don't think "careful" is the word.

Mr. WOLVERTON. More of a procedure such as you have mentioned. We will take a very simple illustration, and it is the only kind a layman can really talk about. That would be the smallpox, or diphtheria, or any of the other vaccines that have come more or less generally in use. Did they have any such similar experience as we are now having with respect to this particular vaccine?

Dr. STANLEY. Having played football, I would like to pass that question to our chairman, because I believe he is competent to answer it, and I doubt that I am.

Dr. PAUL. Mr. Wolverton, I cannot cover the whole subject. But I can state with some confidence that with new vaccines that have been

introduced to the medical profession in my lifetime there has been in high percentage some difficulty and some tragedy.

We have clearly in our memory the vaccination against tuberculosis, the BCG so-called, in which a tragic episode occurred in a city in Germany in 1930. We have in our memory during the war the problem of vaccinating troops against yellow fever where unfortunately, as the term has been used here a "wild virus," or some contaminating virus got into the vaccine and caused a large number of cases of hepatitis in American troops in 1942.

We have memories of the situation concerning diptheria, I think it was in Texas, about 10 years ago.

So that these accidents are not unfamiliar in the development or sometimes in the well developed product.

Mr. WOLVERTON. Is it your opinion that it would be advisable to follow the course indicated by Dr. Sabin, which was expressed a few moments ago? And I would like to know from the other members of the panel. I think it is one of the important questions to decide in view of the fact that we have legislation before us which provides for the distribution of it in large quantities by the Federal Government. Therefore, we should know as definitely as we can from the best advice that is available whether it is the proper thing to proceed immediately, or to wait until January.

We all have a great deal of respect and we acknowledge our indebtedness to Dr. Salk. It has been a wonderful step forward and I agree with Dr. Sabin we do not want to spoil it by utilizing it sooner than might be practicable and for that reason, and to guide this committee in the passing of legislation, I would certainly hope that it would be possible for this panel, which is one of the most distinguished that I think has ever been brought together, to express an opinion to us as to whether the course suggested by him will be the safer one to follow.

Dr. PAUL. I am having recalled to me that I am masquerading under the guise of an impartial chairman. I would rather not discuss the matter at length, but I think I must mention the fact that as a matter of record, I have already written to the National Institutes of Health a letter, dated May 25, 1955, stating that I hoped that at the earliest opportunity the avirulent strains could be introduced into this program.

Now, I would not care to express an opinion whether that would mean a stoppage of the existing program, but I have expressed the opinion that as soon as possible, as soon as practicable, that the substitution can be done.

The letter is in the hands of Dr. Workman, of the National Institutes.

Mr. WOLVERTON. I am trying to put the question in a plain way so I think it could be answered "Yes" or "No." At least, that is the wish I have, that it can be answered "Yes" or "No." After all, these phrases that are used, these terms that are used, are so confusing that I am not able to gather their full significance to the extent the members of the panel would.

However, I could understand if somebody said "Yes, I agree with Dr. Sabin; I think that is what ought to be done." Or if somebody says "No, I don't agree with him," I can understand the word "No" and I can understand the word "Yes."

If somebody would be willing to express an opinion in that way, it would be very helpful, in my opinion.

Dr. PAUL. Well, I don't wish to wiggle out of the direct question, sir. I would like to have it brought out in the discussion what the practical problems are in relation to the decision, if possible.

Dr. ENDERS. Since Mr. Wolverton has asked for an opinion, I will say that I agree, I think, with everything, practically, that Dr. Sabin has said. I think the great point that he made was that we could not predict with regularity that another incident such as we have had would happen on any information that we are now in the possession of.

In view of that situation, I might perhaps review the facts again that he mentioned for the sake of clarity.

One, there has been some doubt cast on the process of inactivation of the virus. We do not know absolutely whether it works according to theory, as Dr. Shannon has pointed out.

Two, the safety test may not be sensitive enough to detect the amount of virus that is sufficient to infect a few human beings who are unusually sensitive.

And, three, we do know that somehow—I think it is fair to say we do know now—somehow in the Cutter case that in spite of the processing, in spite of the safety tests, live virus did get through and was inoculated, with the production of disease.

Now, new safety tests may take care of that. They have not been tried so far as I know. There are certainly additional improvements that could be made along the lines that Dr. Shannon has mentioned.

In particular, the suggestion of the avirulent strain in my view. Indeed, I don't think until that is done I would advise going ahead. I believe I so recommended at a meeting on May 7 in the National Institutes of Health.

I think undoubtedly within a reasonable time we will have a safe and effective product. In view of the facts that have been brought out here this afternoon, it seems to me part of the wisdom to wait a little while until we have it.

Thank you.

Mr. WOLVERTON. Is there anyone else who wishes to say yes or no?

Dr. PAUL. I would like to call on other members of the panel if they wish to discuss this point. I will turn to the gentleman on my left and ask Dr. Rivers how he feels about this matter.

Dr. RIVERS. I could not agree with Dr. Enders and Dr. Sabin. No vaccine has ever had the testing that this one had before it was used last summer, in 1954. I cannot imagine doing more than was done at that time. I can imagine it now.

Certainly with the new regulations that are proposed, I think it would be tragic if we stopped the program now. My answer to you, sir, is that I do not agree with Dr. Sabin.

Mr. WOLVERTON. I can understand that answer perfectly.

Dr. PAUL. Dr. Smadel?

Dr. SMADEL. One of the most difficult decisions in this kind of problem is when do you stop doing research and start using the material that you have already produced.

It is always possible to improve the material that you made yesterday and the things that have been suggested today no doubt will improve the vaccine and I expect that they will be put into effect.

I would like to leave with the commitee, though, the idea that no one at this table can predict when any of these things can be put into effect. We can hope, but each time one changes the procedure, each time one increases the amount of material that is manufactured, then one runs into new difficulties that one cannot foresee at this time.

So one is left, then, with the ultimate decision, "Shall we use what we have now, or shall we wait an indefinite period, 3 months, 6 months, 5 years, until we have something which we think is perfect at that time, and then use it?"

In my opinion, we should not wait.

Dr. PAUL. Dr. Salk, would you care to speak to this point, please?

Dr. SALK. I will not express an opinion relative to the question.

I do, however, want to make some comments on what appears to be the basis for the thinking one way or the other, and the basis for the thinking happens to be the mystery about the Cutter incident.

The implication has been left that we do not know what happened there, nor do we have any way of being absolutely certain that it will not happen again.

It seems to me that Dr. Sabin's statement that the Cutter vaccine given to children had been tested negatively should be countered by the fact that Cutter vaccine given to children has revealed the presence of live virus in laboratory tests.

All of these considerations, it seems to me, should be made available to those who make the decisions.

I have in the past contributed in nowise to making administrative decisions, and I prefer at this point merely to remain in my role of investigator who provides the facts and the evidence upon which others who have administrative responsibility can then decide.

I feel the problem has gotten to the point where it is now in the area between the manufacturers and the National Institutes of Health and those who are interested in the problem, but their interest is of a slightly different magnitude now that the investigation has moved from research into application.

Dr. PAUL. Thank you, Dr. Salk.

The CHAIRMAN. May the Chair inquire. The bells have rung for a rollcall in the House on the passing of a bill. It is necessary for the subcommittee members to go to the floor.

The Chair understands that Dr. Paul can be here again tomorrow. Can all members of the panel be here at 10 o'clock in the morning? That seems to be unanimous.

Mr. WOLVERTON. May I inquire whether we will continue where we are leaving off this afternoon?

The CHAIRMAN. That will be in order. The committee will stand adjourned until 10 o'clock tomorrow morning.

(Thereupon, at 3:40 p. m., the subcommittee was recessed, to reconvene at 10 a. m., Thursday, June 23, 1955.)

POLIOMYELITIS VACCINE

THURSDAY, JUNE 23, 1955

HOUSE OF REPRESENTATIVES,
SUBCOMMITTEE ON HEALTH AND SCIENCE OF THE
COMMITTEE ON INTERSTATE AND FOREIGN COMMERCE,
Washington, D. C.

The subcommittee met, pursuant to recess, at 10 a. m., in room 1334, New House Office Building, Hon. J. Percy Priest (chairman of the subcommittee) presiding.

The CHAIRMAN. The committee will come to order.

Before proceeding with the panel discussion this morning, I want to say just a word or two in order to reemphasize what I consider to be the responsibility which this committee has and the responsibilities which I believe belong elsewhere. This committee has, as you know, before it, legislation requested by the President and the Secretary of Health, Education, and Welfare to authorize appropriation of funds, first it was $28 million, later raised to $35 million, to assist the States with mass polio vaccination programs by providing funds for those children whose parents might not otherwise be able to pay for the vaccine.

This committee, therefore, has the responsibility to decide whether this legislation should or should not be reported to the floor of the House. Of course, this decision involves scientific questions relating to the safety and effectiveness of the vaccine which is to be used. It is for that reason that I have requested the formation of this panel in order to advise the committee on this question.

On the other hand, I want to point out, as I see the situation, this committee does not have the responsibility nor could it ever hope to discharge the responsibility, of determining what the minimum requirements should be which the Public Health Service should insist upon with regard to the manufacture of any particular vaccine.

Also, the committee could not hope to decide whether the protein matter remaining in the vaccine should be strained out by manufacturers or can safely remain in the vaccine.

Nor could the committee decide, once a vaccine meeting these requirements is available commercially, whether individual physicians should or should not give the vaccine to children. Furthermore, this committee could not hope to decide what age groups of children should be preferred over what other age groups.

Finally, this committee does not have the responsibility of determining whether any private organization should or should not go ahead with any program for the vaccination which it may have.

I am aware, of course, that the testimony which was presented here yesterday and which will be presented this morning before the com-

mittee will no doubt have indirectly some effect on these other determinations which the Public Health Service, individual physicians, private organizations, and last but not least, the parents of this country will have to make. However, I want to make it abundantly clear that the responsibility which this committee must discharge is with regard to legislation now pending before us, and I hope that the committee will be in a better position after these hearings have been completed to discharge this responsibility than it would have been had we not had the benefit of this very, very fine panel discussion.

I wanted to make that position of the committee clear for the record at this point.

Now, Dr. Paul, when we adjourned yesterday Mr. Wolverton was questioning some panel members. Mr. Wolverton who is member ex officio of all subcommittees, for the moment is not present, but the ranking member, after Mr. Wolverton, of this subcommittee is Mr. Heselton. He had one or two questions I believe he wanted to direct to Dr. Enders this morning before we proceed with your agenda.

Mr. Heselton, you are recognized at this time for that purpose.

Mr. HESELTON. May I emphasize what our chairman has so well said. There is absolutely no politics in this as far as the Republican side is concerned. We know our chairman, and have known him for years. We respect his integrity, his ability, and his determination to help us reach the proper decisions in our proper field. We recognize the limits of the field. That is why we are so appreciative of having such an eminent panel delineating what we can do and what we should not do which would be harmful to the program.

I did want to make that comment in the presence of the press and the panel, and of the persons who are in the audience, because I feel Mr. Priest is entitled to the recognition of the excellent farsighted and constructive efforts which he has made to develop through these hearings a forum for you gentlemen which can be of lasting importance to the American people in terms of this very important problem.

Dr. Enders, I express my apologies. I was tied up in the Rules Committee until after half past 12 yesterday. I did read with care the comments in the morning press, which leads me to a few questions.

I take it that there developed toward the end of the hearing some differences of opinion among you gentlemen—honest differences of opinion—as to whether the program should continue or whether there should be a period of suspension during which a so-called safer vaccine might be developed.

I recall on previous occasions when I attended the first conference at the Department, the emphasis placed on safety by the Department, which I thought was very well taken. I think the panel would agree to that.

As I understand it, you subscribe to Dr. Sabin's statement. Am I right about that?

Dr. ENDERS. I supported Dr. Sabin's statement; yes, sir.

Mr. HESELTON. As I further understood—and I want to come back to you, Dr. Enders, for one more question—and I am going to make this a general question—in view of our uncertainty as to whether Mr. Wolverton can be here to carry on his interrogation, I am not going to trespass upon what he has undertaken to do; which may leave our record a bit clearer and be of assistance to us.

May I ask if any other members of the panel who have not yet expressed an opinion one way or another, as to whether the program should be continued as it has been started or whether it should be suspended for any period of time in order to achieve what might be a safer vaccine, care to express themselves on that point at this time?

Dr. Paul, do you know of any other members of the panel who wish to speak to this matter?

Dr. PAUL. May I answer that question?

Mr. HESELTON. Yes, sir.

Dr. PAUL. It is our plan this morning to proceed exactly as we left off yesterday afternoon when Mr. Wolverton requested that the panel be polled as to whether or not they agreed with Dr. Sabin.

Mr. HESELTON. I realize the press, with all its good efforts, is limited in the space it used. I did not catch that particular information and that is why I asked the question. That being the case, I withdraw the question and leave it to the procedure you have developed.

I would like to ask this; I am not clear on this. Possibly some other members of the committee are. I do not know whether the information has become available or is likely to become available before long. Is there any way of determining how far the country has gone in terms of the vaccination? I take it there are three vaccinations: The first two would be completed by a fairly early date, and perhaps have been completed; the third is the one that would be undertaken, as I understand it, in the fall.

Can you give us any information as to how far the country has gone on point one, the first two vaccinations?

Dr. PAUL. I would like to turn that question to Dr. Shannon.

Dr. SHANNON. I think actually Dr. Rivers could give a more precise statement because the vaccinations up to the present time have all been conducted, or essentially all, under the NFIP program.

Mr. HESELTON. By what?

Dr. SHANNON. The National Foundation Infantile Paralysis program. I am sure he would have much more precise information than I would.

Mr. HESELTON. We would be glad to hear from him.

Dr. RIVERS. Sir, I am afraid I cannot give you precise information. As you know, two inoculations are required this summer. Then a third inoculation is required several months later, following the second inoculation.

Approximately there were to be about 9 million children vaccinated this summer with the first and the second inoculations. To the best of my information I would say there are somewhere between 6 and 7 million children who have received the first inoculation. I can't say that is an absolute accurate figure, but that is in the neighborhood of the figure.

In other words, there are some children who have as yet not received the first inoculation. I think some in New Jersey have not. I think some in the more northerly States have not yet received their first inoculation.

So it means that probably 1 or 2 million children are yet to receive their first inoculation this summer, and practically all of the 9 million children are yet to receive their second inoculation. Those are approximate figures; I don't know whether anyone at the moment has absolute figures.

Mr. HESELTON. Doctor, may I ask you one question as to your answer? Of those approximately 2 million who have not received the first inoculation, are they scattered around the country or are they concentrated in a certain area?

Dr. RIVERS. Some of them are children who refused. That is, no child is inoculated unless the parents request it. Some of those children the parents have not requested it. The others are largely in the Northern States, as I understand it, because the program was started in the Southern States due to the fact that poliomyelitis starts in the Southern States first and marches north. I would say most of these children that are not vaccinated are in the more northerly States.

Mr. HESELTON. Are you able to give us any estimate of how many approximately of 2 million are likely to receive the first shot soon?

Dr. RIVERS. I didn't understand the question.

Mr. HESELTON. Are you in a position to give us any estimate as to how many of those 2 million, approximately, who as I understand it have not received the first shot, are likely to receive that vaccination soon?

Dr. RIVERS. There, again, I think Dr. Shannon is in a much better position, if anyone is in a position, to say how soon any vaccine will be released. I have some grapevine information, but I don't think that kind of information should be given to you. I think Dr. Shannon is the one who should give it.

Dr. SHANNON. I cannot give you any precise information on that, sir, except to say that Dr. Scheele's committee on poliomyelitis vaccine, which has the responsibility of recommending to him lots which are suitable for release, will have before it in the course of the next 24 to 48 hours a number of lots of vaccine. I have not had the opportunity to have their opinions on the suitability of each lot, so I am not in a position to say whether sizable amounts will be available shortly or will not.

I am very sorry, sir, but this is a matter for them to reach a judgment on and to advise Dr. Scheele. They have not met on the batch that will be shortly available.

Mr. HESELTON. Dr. Paul, may I ask one concluding question—and I do not know by whom it should be answered. Let me put it this way: I read in the press account a statement by somebody to the effect that he hoped the future developments in terms of Salk vaccine would receive wider dissemination among the physicians through their technical journals. That is, physicians and scientists. Is that program now progressing so that you are satisfied the family physicians around the country are going to be reasonably well informed as to developments and what should be done and what should not be done in the near future?

Dr. PAUL. I, too, have the hope that it will be done. It seems to me that there is a reasonable possibility. This program has gone faster than the journals have been able to keep up with it. The point was made yesterday, I believe at this end of the table somewhere, that we had not been able to keep pace in informing all physicians.

All I can do is express the belief that there are many here in the panel who have felt that that was true and that the sooner this information would get into the legitimate, proper sources of medical literature, the better. I think I express the opinion of the group on that.

Mr. HESELTON. Thank you, and all members of the panel.

The CHAIRMAN. Dr. Salk.

Dr. SALK. I don't want to discuss this point or belabor it, but merely to say that there are implications in the comments by Dr. Paul and others to which reference was made yesterday. There are a number of papers that have been published and there are a number of papers in press—the precise number or their dates I could provide for you—and this subject was discussed at great length, I understand, at the meeting of the American Medical Association; and when the facts were put before them I believe they withdrew their objection that insufficient information was published.

It is true that the information submitted to the Journal of the American Medical Association for publication was not always accepted by them because they regarded some of the material either too technical or too highly specialized.

I wish to call your attention to the fact that publications invariably lag behind the progress of work. Were it not for the fact that time was taken by many who are involved in this in matters outside of their precise scientific area much more information would have reached the scientific literature and undoubtedly will soon in a great flood.

The CHAIRMAN. Dr. Salk, you mentioned that you could furnish—and I would not want to have you attempt to do that at this time—a list of the publications that have been made up to this time?

Dr. SALK. Yes, indeed. If you would like me to recite any at this time I will.

The CHAIRMAN. If you can furnish that for the record it will be quite all right.

Dr. SALK. Yes, sir.

(Information referred to was placed in the committee files.)

The CHAIRMAN. Dr. Salk, we turn back to you for a continuation of whatever program you may have this morning on the agenda.

Mr. SPRINGER. Mr. Chairman, may I ask a question? Are we to assume that no further questioning is going to take place at this point?

The CHAIRMAN. If you have questions, you may proceed.

Mr. SPRINGER. I would like to direct this question to Dr. Shannon: I have been told that even this early in the polio season there is evidence that the incidence of paralytic polio is lower among children who have received the shots of Salk vaccine than among unvaccinated children. This is said to be particularly true in Southern States where the polio season begins earlier. Dr. Shannon, is that a fact?

Dr. SHANNON. I cannot tell you, sir. I have not seen the breakdown.

Mr. SPRINGER. Is there anyone on the panel who has the information?

Dr. BERGSMA. I have not seen the data because it is constantly changing, but I have heard from certain people who have studied it in considerable detail and the impression I got from hearing their discussion of it was that the figures do show such a trend.

Mr. SPRINGER. Dr. Francis, you evaluated the results of the 1954 field trials and you found the vaccine to be 60 to 90 percent effective, according to your report, which was made on April 12 of this year; is that correct?

Dr. FRANCIS. Yes, sir. I think that is to be part of the later item on the agenda.

Mr. SPRINGER. I think this has almost got to follow here if we get at the points that have been raised. This line of questions has almost got to follow what has been said by Dr. Sabin. These are only lead-up questions.

Will you tell this committee what is meant by 60 to 90 percent effective?

Dr. FRANCIS. Essentially it would be this. If there were 100 cases, let us say, in the controls and there were something in the range of 20 cases in the vaccinated, then that would come within a general range of 80 percent. In other words, you have prevented 80 cases out of the expected 100. That is the general concept.

Mr. SPRINGER. Now, Doctor, based upon that study of an average of 80 percent effectiveness, that in effect means that 20 percent of those inoculated are not immunized by this polio vaccine. Is that a correct statement?

Dr. FRANCIS. That would be 20 percent of the expected number.

Mr. SPRINGER. And 20 out of each one of those 100 inoculated could receive polio from some other sources? In other words, they could receive polio in the natural course of getting it as anyone else could who had not been vaccinated?

Dr. FRANCIS. Presumably.

Mr. SPRINGER. I want to be sure this is in the record and straight. There is no contention that this polio vaccine is 100 percent effective upon anybody who has received the inoculation?

Dr. FRANCIS. We have never so contended. We have merely stated the evidence we have obtained.

Mr. SPRINGER. Your report so shows?

Dr. FRANCIS. Yes, sir.

Mr. SPRINGER. In your report—and I cannot find the page, but I believe I am stating it accurately—during the last 20 years the number of polio cases arising each year has varied between 35,000 and 50,000. Is that a fair statement?

Dr. FRANCIS. I believe that is what Dr. Sabin referred to yesterday. I don't know that we quoted it in any specific paper.

Mr. HESELTON. In respect to your answer to Mr. Springer's questions as to the effectiveness of 80 percent, have there been any studies made for inoculation of other types of diseases as to how effective they have been percentagewise?

Dr. FRANCIS. Yes.

Mr. HESELTON. Can you give us any information as to what the average success is?

Dr. FRANCIS. I don't know in terms of specific figures, but the studies that were done with whooping cough were the ones that were very carefully studied and are still being studied in a combined fashion. The study with influenza vaccine was carried out in 1942, and since then in the Armed Forces, was also done on a very controlled basis which would show that had been in the range of 70 to 75 percent effective against the epidemic disease at that time.

Mr. HESELTON. Then it is a fact that Dr. Salk's vaccine at this date is more effective?

Dr. FRANCIS. I don't think you can say that.

Mr. HESELTON. Would you say equally effective with any other vaccine that has been developed for any other disease?

Dr. FRANCIS. I don't think you can say that necessarily because the general experience with adequate smallpox vaccination is very highly effective. And the same is true of diphtheria. I don't think we ought to be debating 5 percent here or 10 percent here.

Mr. SPRINGER. Now, Doctor, this question: First, assuming that there will be 35,000 cases of polio in the United States in 1955, assuming further that 10 million children in the most susceptible age groups could be immunized this year, how many cases of polio might thereby be prevented if this vaccine were used in 1955?

Dr. FRANCIS. I couldn't give you that kind of figure offhand. I would have to sit down and do some calculations.

I am not sure I can calculate it with those presumptions.

Mr. SPRINGER. Doctor, I am going to come back. I do want you to calculate it and give us at least a rough figure.

Let me ask you this question: Would the prevention of polio be substantial?

Dr. FRANCIS. I would assume so, if the vaccine had the same degree of effectiveness that was observed in 1954.

Mr. SPRINGER. It would mean, Doctor, the prevention of several thousand cases, would it not?

Dr. FRANCIS. I would think so.

Mr. SPRINGER. That is all. I want to come to Dr. Sabin now.

Dr. Sabin, if over the next several months the amount of paralytic polio among children who have received one or more shots of Salk vaccine proves to be significantly less than the amount among other children denied the vaccine, would you be willing to take the responsibility for stopping the progress of this immunization for 1955?

Dr. SABIN. I have taken full consideration, sir, of this possibility.

Mr. SPRINGER. Let me come to just 1 or 2 other figures. This is still for Dr. Sabin.

According to the figures which I have before me—and I am excluding the Cutter group from that, Doctor—there were 4,535,678 inoculations among laboratories B, C, D, and E. According to the figures I have, among those laboratories there were 59 cases of polio. According to further figures I have, that is an incidence of 1 case in 92,261. Are you still willing to stand upon your statement of yesterday based upon those figures as to the possibility of incidence if this program were continued?

Dr. SABIN. Mr. Springer, your questions are very much to the point. I wish very much that the answers could be as equally clear. I wish it were possible to make the answers as clear as your questions are clear; but I am afraid they are not.

I have indicated in my introductory remarks yesterday morning that in this country the chance over a lifetime of acquiring paralytic polio—and that includes the mild as well as the severe cases—may vary in different parts of the country, roughly from one in a hundred to one in a thousand. Divided over the years, again very roughly—let us say over the period of 30 years—that would mean that one would have a chance in a lifetime of having polio in any one year perhaps 1 in 30,000 or 1 in 20,000. I am sure that could be argued, because for different ages it would differ considerably.

So that the decision is not an easy one, sir. When you say to decide between a chance of 1 in 30,000 and 1 in 90,000, it is very difficult indeed. I am in full sympathy with those who want to prevent as much polio

as possible as soon as possible. There will not be, we know, enough vaccine to protect all those who need vaccine this summer. So it will not be possible to cover the country as would be desired. Therefore, we will not be able to achieve the maximum protection for the largest number who need it.

Mr. SPRINGER. I am not going to belabor this question, but I do want to see whether or not it is your belief that if this program were continued during 1955, and we will say that several thousand children could be prevented from getting polio by virtue of the inoculation under the present program, do you believe then that the program should be discontinued?

Dr. SABIN. It should not be done because of the uncertainty that any lots that have not as yet been used will be as safe as the vast majority of the lots that have been used thus far. Because of the uncertainty that the difficulties that we have encountered before can definitely be avoided in the future.

Mr. SPRINGER. Doctor, may I ask this one further question; and I think I am finished. As to laboratories B, C, D, and E, are you satisfied with the effectiveness of their program?

Dr. SABIN. I must again qualify my answers by the remark that there can be no absolute certainty. It is my belief that the drug manufacturers have expressed the opinion publicly that what has happened to Cutter's and in 1 or 2 instances to the Wyeth laboratories might just as well happen to them. It was difficult to predict.

The assumption that the vaccine now is as safe as science can make it is not a correct assumption. It can be made safer. People are now at this instance doing work to make it safer. That is why it is difficult to single out laboratories B and C and differentiate them from laboratories under categories.

Mr. SPRINGER. Let me ask you this one last question: Do you believe that even with an improved vaccine that your rate of incidence was going to be less than 59 cases in 4½ million injections?

Dr. SABIN. May I point out that these 59 cases to which you refer are cases that one would always expect to occur. I do not believe that they have anything to do with the vaccination at all. They are cases that occurred because the vaccine could not have provided immunity. That will always occur. I think they have nothing to do with vaccination and cannot enter into these considerations. The only cases that can enter into these considerations are the approximately—and again I don't have the figures with me—60 cases of paralysis that have occurred in Cutter inoculated children, the forty-some-odd cases that have occurred in members of their family. I don't know how many have died yet.

It is a very difficult moral issue to say to any one parent—I am saying it to myself, too; I have young children myself—shall I ask them to take the chance of acquiring polio this year, which they might not have, simply because by doing this a large number will be protected? Because I have every belief that a larger number will be protected. Whatever arguments there may be as to whether it is 60 or 80 or 90 percent effective, Dr. Francis' report has shown that there is a definite effectiveness. So I have no doubt there will be protection.

But I cannot ask anyone to come forward and take the chance this year of getting paralytic polio which he otherwise might not have, be-

cause in so doing he would be doing a great service for perhaps 2,000 others who would be prevented from getting polio this year.

That does not mean that they would be prevented from getting polio 3 years from now because no one now knows how long the immunity they will acquire this year will last. If they don't get it this year, they may still get it 4 or 5 years from now.

Mr. SPRINGER. Thank you, Doctor. That is all.

Mr. HAYWORTH. I would like to inquire whether or not the cases that have developed because of infection from vaccine have been more or less severe than cases that on the average normally developed in the usual procedures of living?

Dr. PAUL. I will turn to Dr. Shannon again.

Dr. SHANNON. I am terribly sorry, sir, but I was reading something hereand missed your question.

(Question read by the reporter as recorded.)

Dr. SHANNON. I am not a clinician and would not be in a position to give an estimate of that. I might say that the portion of cases with paralytic polio would appear higher than are usually reported in an ordinary zone. But the significance of that in relation to the type of epidemiological followup, the significance of that in terms of the positive attempt or the positive measures taken to exclude cases that were not polio, which in the ordinary circumstance does not obtain, could have such a drastic effect upon those figures that I don't believe that they are very meaningful in comparison with figures conventionally collected from simple reporting of physicians through normal public-health channels.

So, while I am not a clinician but I would say that the figures are so weighted they are impossible of comparison with figures collected in prior years.

The CHAIRMAN. If there are no further questions from the committee, you may proceed, Dr. Paul.

Dr. PAUL. Dr. Francis has first asked me whether Mr. Springer would like to hear from him at this point about those calculations.

Mr. SPRINGER. I think it would be well to put that in the record, Mr. Chairman, if you would defer for a second?

The CHAIRMAN. Very well.

Dr. FRANCIS. I would like to emphasize that these are very rounded figures.

Mr. SPRINGER. I understand.

Dr. FRANCIS. You proposed there would be 35,000 cases this year. I have taken a general estimate of 70 percent of those cases being under 20 years of age. I think that would not be too greatly out of line. This would leave 24,500 cases at that level.

If 60 percent of them were paralytic, which might be in keeping with our data from last year, that would have 14,700 paralytic patients. If there were 80 percent protected, I would presume there were 11,760 that were protected; if 70 percent protected it would be 10,290 out of the 14,700. As I say, these are very general and rough estimates at the best.

Mr. SPRINGER. Thank you, Doctor.

The CHAIRMAN. Dr. Paul.

Dr. PAUL. I want to thank Mr. Priest particularly for reminding the panel as to the nature of our problem. That we are here concerned

with attempting to supply him with scientific information quite apart from many of the other problems that come into the question of poliomyelitis vaccine assistance legislation.

I also want to point out briefly that what we will be discussing and voting upon is a problem of calculated risk. This problem comes to every clinician who treats sick patients a dozen times a day. There are dangers in doing this, there is good in doing this; there is no arbitrary answer. It is a question of calculated risk.

Usually one does this in a consulting office. Today the sick patient represents more than one sick person.

The proposal which Mr. Wolverton made yesterday I shall try to restate and I hope Dr. Sabin will correct me if it is not given properly. This was to the effect that avirulent strains of poliomyelitis be substituted in the next vaccine for the strains that are now being used and that this be done as soon as possible and the current vaccination program be terminated with the hope that it can be taken up as soon as the substitution is made, presumably—these are my words—next fall or next winter.

Mr. Wolverton put the question how many agree or disagree with Dr. Sabin. I am going to ask him whether this is correct, but before doing so I wish to point out that as was brought out yesterday in the discussion, there are at least two questions here.

One of these questions is, that an early substitution of the avirulent strains be made as soon as possible. The second question was that of terminating the vaccination program until this be done.

Is that correct, Dr. Sabin?

Dr. SABIN. Mr. Chairman, I would ask that for the record only one word be changed, and that is instead of using "avirulent" because that requires many scientific qualifications, that the word "attenuated" be substituted.

Dr. PAUL. With that preamble, I will proceed, as we did yesterday, unless there are members of the panel who would like to speak at this point.

Dr. HODES. Dr. Paul, I would like to ask several questions of Dr. Shannon regarding the new testing. I think it will influence a good deal my thinking on this point and perhaps others.

I would like to know first, Dr. Shannon, what percentage of lots tested by the new testing that you spoke of yesterday have been shown to be positive. The figures you gave us, I think, ranged from 4 percent to 33 percent of those tested by the old method by the manufacturers were positive. What is the score with the new testing, if they have been tested that way?

The second question is: Have any of the vaccine lots which passed the old test been subjected to the new testing procedure, and if they have, what have been the results?

Thirdly, have all the vaccine lots which are now being injected into children been subjected to the new test for presence of virus?

Dr. SHANNON. In terms of percentage of lots tested by the new test which are now available, the answer to that is very simple, there are none. The new test involves the introduction of control procedures incidental to the very processing of the vaccine. It should be appreciated that it requires roughly 2 weeks to process a single batch through the period of inactivation. It requires an additional 2 to 4

weeks to conduct the final tissue culture test. The vaccine is then combined into a trivirulent pool which is the ultimate vaccine and the final tissue culture test which again involves an additional 2 to 4 weeks.

I do not recall the precise date, but, as I recall the minimum requirements were changed as of about June 1. I have been told by Dr. Francis it is the 27th of May. At this time there was general agreement from the industry that they would accept these requirements and produce from here on by that method.

Meanwhile the committee sat with each of the manufacturers and went over each of their production lots and advised them on how they could handle vaccine at the various stages of development, so as to bring that up as close as was possible to the measure of confidence that this processed vaccine under what we would call interim clearance procedures, to that one would have in a material that was started after the 26th or 27th of April.

That really answers the second question, too, which is have any of the vaccine lots which passed the old test been subjected to the new test and, if so, what results were obtained.

The new tests involved analyses in these interim control periods of relatively large volumes. Depending upon the stage of development is determined the volume and the number of repeat tests. To date those that had passed up to that stage in the protocols I have seen have passed the superimposed secondary more safe test procedures. But I would say that the number of lots that we have examined are relatively few. It remains for the future to determine the extent of discard or passage of routinely produced material.

Then that answers the third question, the material being injected into the children now has not been produced under the amended requirements. The material under those requirements presumably will not be available until sometime around about, I would guess, the end of July or perhaps early August. The material that is available now and will become available in the coming weeks will approximate in degree of safety as best as it is possible the material which will be produced at a later time under modified requirements.

Dr. MAYER. May I ask another question, Dr. Shannon?

Have any of the incriminated lots of Cutter been tested by the new procedures involving large volumes, and if so, what results have been obtained?

Dr. SHANNON. At the present stage of development of that testing program, which is tantamount, as you will appreciate, to a very sizable research program, the initial test program has been to examine a fairly large number of both the crude vaccine and filling lots by a variety of procedures, many of which are truly research procedures rather than routine. These research procedures have turned up, as you know, positive virus in a number—as I recall it is either 3 or 4 at the present time—lots of vaccine. We have not had at the present time sufficient volumes, although these volumes have been requested of industry, for a type of testing program that would simulate the type of testing program now being applied to the industry.

I point out again, though, that the results of a testing program of that sort will not be a very firm basis for action. I think we have certain information to date that leads us to suspect certain areas in the total production of this vaccine which is under analysis at the present time.

If the final definitive answer is one way, then I think that the test you propose might be crucial. If it is another way, it would be hopeless. We are in the unfortunate situation here of trying to do what Henderson at times said cannot be done, that is, to prove the absence of live virus, rather than proving it is present. Having proved it is present, we are in a realm of "quantitation" which precludes a positive answer that would be helpful to our present deliberations, I am afraid.

Dr. PAUL. We want to curtail our discussion somewhat, but anything that concerns our ability to arrive at a better decision before we poll the panel I think should be brought out at this time.

Dr. SALK. I merely want to ask Dr. Shannon, since he conveyed the impression that the retests of some of the Cutter material with a test less sensitive than the one proposed, has thus far in some instances revealed the presence of live virus in certain batches of Cutter vaccine.

Dr. SHANNON. I cannot answer that question directly. I can relate one test that involved a very small amount of virus in terms of total volume. But this virus was concentrated twenty-five fold. This came up as a positive tissue culture in a relatively small volume. But this, as I say, is at the present time a research procedure and is not applicable to a consideration of the routine large volume test as currently applied by industry. In toto the volumes of samples that have been tested in a number of laboratories, if one adds up the total which is one of the points of view expressed by this testing program, has been disappointing in the amount of live virus it has shown up on tissue culture tests.

But again I would look upon this as something quite different than the simple routine mix of a test on a series of batches of vaccine in order to provide the answers we all would like to have.

The cracking of this thing down has to be done in stages. As you all know, each stage takes a sizable length of time and one cannot take the next step until the information is in from the first.

I think certainly our own technical committee is as impatient as I for results on which they can base action. Unfortunately those results are not available nor will they be available in toto for some time.

Dr. SALK. Mr. Chairman, I should like to make just one point.

Mr. Priest has indicated that the purpose of these hearings and this panel discussion is to do something about increased public confidence by making them aware of the facts. I think it would be of some comfort to some to know that in fact the incriminated lots of Cutter vaccine have revealed in the laboratory the presence of live virus. This fact would be somewhat helpful to those who may be confused by the impression that we do not know what happened. In fact the laboratory has revealed the presence of live virus in Cutter vaccine and therefore this is all not completely mysterious.

Dr. PAUL. Mr. Priest, I would like to inquire about time at this point, because I know you have intimated that some of the committee members will not be able to remain all morning and perhaps they would like to hear our vote. I want to have your opinion about that, sir. Is it important for us to poll the members soon or shall we continue our discussion?

The CHAIRMAN. I think it would be well to continue the discussion if there are others who wish to enter into the discussion, Dr. Paul.

I would not want to cut off anyone who had anything to contribute to the discussion. I leave that to your discretion and the judgment of the panel.

The committee is entirely willing to go along with either procedure.

Dr. PAUL. I think we will proceed for a short time with the discussion of the problems, althought I hope we can proceed with the poll presently.

Dr. MAYER. May I ask a brief question from Dr. Shannon again? I take it, Dr. Shannon, from what you have said, that the new testing procedures would be very likely to have detected the defective lots of Cutter vaccine. Is that essentially correct in your opinion?

Dr. SHANNON. It is my conviction, yes.

Dr. SMADEL. Mr. Chairman, may I suggest that the reason for this panel being here is to advise Mr. Priest and the other members of his committee. It is not primarily the concern of this panel to educate some of its members and to provide them with information which they should have had. That we could have done before or we can do at a later date.

Dr. PAUL. Is there any further discussion?

Dr. HODES. Dr. Paul, if Dr. Smadel is right, then there is not much point in going on with the discussion. Is that a correct statement?

Dr. SMADEL. That is my understanding.

If you do not have information on this, then your vote on the matter is not particularly relevant.

Dr. HODGES. That is probably the position I am in.

Dr. SMADEL. Admittedly.

Dr. MAYER. All the information may not have been made available.

Dr. PAUL. Dr. Stanley?

Dr. STANLEY. Mr. Chairman, I have served for several years on the Council of the National Acadamey of Sciences, and I know the genesis of the committees that they have set up at the request of Government. Hence, I have some knowledge of the philosophy which resulted in the setting up of the present panel. I think this should be clearly understood; otherwise, I think there is a real chance for misunderstanding.

I would guess that in the selection of this panel that Dr. Bronk tried to bring to the panel experts in different fields without reference to any opinion which they might hold with respect to the stopping or the proceeding with this program.

The CHAIRMAN. May the Chair state that that is his understanding of the basis for the selection of this panel.

Dr. STANLEY. That being the case, therefore, there are certain of us, in my own particular case being a chemist, I would want to disqualify myself. As a chemist I have certain opinions. As a medical man, obviously, I can have no opinion. So that this voting as to whether you proceed or stop really—and again this is my opinion—is not completely relevant because you could take any number of medical scientists and by selection you can get a preponderance on one side or a preponderance on the other side.

In the particular case, the selection was based upon expertness in different fields. Like Dr. Mayer, an immunologist, the gentleman on my right a public health officer, myself a chemist, Dr. Rivers, and so forth.

I wanted to state this for the record, because I believe it is important in view of the fact that Mr. Wolverton is pressing for a vote.

The CHAIRMAN. May the chair just state with further reference to what you have said, that when Dr. Bronk was asked to assemble for the benefit of the committee a panel for the discussion of these questions, the purpose of the request was just as you have stated. I want that made also a part of the record at this point.

Dr. PAUL. Thank you, Dr. Stanley.

The CHAIRMAN. We want to get the best testimony from men whom we have reason to believe are right at the top in the various fields in which they engage.

Dr. PAUL. At this point, I think it might be worthwhile to review yesterday's opinions given by 4 or 5 individuals, one of whom was not present at this meeting. I have resolved their opinion into the two questions which I have spoken of a few minutes ago.

The first question was substitution of attenuated strains of virus as soon as possible. The second one dealt with the termination of the program as it now exists until that substitution be made.

As I understand the votes and recorded them here, Dr. Sabin was in favor of both of these suggestions. Dr. Hammon, whose letter he quoted, was also in favor. Dr. Rivers was in favor of substituting strains as soon as possible but was not in favor of stopping the present program. Dr. Smadel expressed a similar opinion to Dr. Rivers. Dr. Enders expressed an opinion similar to Dr. Sabin. Dr. Salk felt that he should not enter into the question.

That brings us around the table next to Dr. Bergsma, who I am sure has handled these problems before.

Dr. BERGSMA. In order clarify my position, I am a physician, and I am a State health officer. On that basis my answer to question No. 1 is "Yes." My answer to question No. 2 is "No."

Dr. PAUL. Just to be sure for the record, you are not in favor of stopping the program?

Dr. BERGSMA. That is correct, I am not in favor of stopping the present program. I am in favor of improving the present vaccine when that is feasible.

Dr. PAUL. Thank you, Dr. Bergsma. Dr. Stanley, I think you have given us your position. Would you care to comment further?

Dr. STANLEY. May I ask if you think my opinion is worth anything?

Dr. PAUL. We honor your opinion very much, sir.

Dr. STANLEY. In order that there is no misunderstanding, I can only take the laboratory results which indicate the uncertainty of the inactivation. I believe that there is still uncertainty which should be clarified in the laboratory. That is as far as I can go on the statement.

Dr. SALK. Dr. Paul, I was passed up before. May I say when you are through polling, I would like to make a remark.

Dr. PAUL. Do I understand, Dr. Stanley, you would care to give an opinion on the substitution of strains or not?

Dr. STANLEY. As a virologist, having worked with viruses for a long time, I recognize the desirability of substituting the attenuated strains in the vaccine.

Dr. PAUL. Thank you.

Dr. Mayer?

Dr. MAYER. I think I am in a position similar to that of Dr. Stanley. I am not a medical man. I am a biochemist. I am an immunologist. It is my feeling that as far as the substitution of an attenuated strain for the Mahoney strain is concerned that this is highly desirable and should be done just as soon as possible.

I would also like to say that I disagree very thoroughly with those who say that this vaccine is as safe as it can be. I think it can be made a lot safer. There has been talk about making it safer for a long time, and I think it should be done just as soon as possible without further delay. But I am not competent to say, since I am not a medical man, whether you should stop inoculation.

Dr. PAUL. Dr. MacLeod?

Dr. MACLEOD. I do not think there can be any question of the desirability of substituting the attenuated strains for the present highly virulent strains in the vaccine formulation. However, it seems to me that the weight of evidence from vaccination programs that have already been carried out is such that it would be wrong at the present time to discontinue the present program.

Dr. PAUL. Dr. Horsfall?

Dr. HORSFALL. Mr. Priest, I am very happy that our chairman had the foresight to break down the package offered us yesterday into its two constituent parts, for otherwise I should not be able to reply "Yes" or "No."

With regard to the hope that it may be possible to substitute attenuated or mild strains, I think all of us are in agreement and I would certainly vote that this be done if it is shown that they are equally immunogenic and will produce as much effective immunity as have the strains so far used.

However, regarding the question of stopping the program, I would vote "No."

Dr. PAUL. Thank you, Dr. Horsfall.

Dr. Shannon?

Dr. SHANNON. Actually the Public Health Service has expressed its opinion with which I concur. This opinion believes that the present vaccine is sufficiently safe for use but would emphasize that no vaccine is 100 percent safe or 100 percent effective. However, it would appear that the risk of acquiring poliomyelitis from an unsafe lot of vaccine tested under the revised standards is very slight and much less than the risk of developing paralytic poliomyelitis from natural infection.

We recognize the need to find substitute strains that are more suitable for inclusion in a poliomyelitis vaccine, more suitable than those currently in effect, with particular emphasis on finding a substitute for the Mahoney strain.

The CHAIRMAN. Dr. Shannon, could I interrupt you? And I am reluctant to do so at that point. I have read in 1 or 2 newspaper articles with reference to a vaccine made in Denmark which stated that they do not use the Mahoney strain. Possibly there are some other countries abroad that are developing or using a vaccine without using the Mahoney strain and that use an attenuated strain.

Could you comment at this point on that particular question, whether that is true or what the results have been?

Dr. SHANNON. This is partly true, sir. In Denmark during the present year they are attempting to vaccinate all children up to some

given age. At what level I am not sure. I believe it is age 20. They use a strain of type 1 virus which is called the Brunhilde strain. This could not be considered to be an attenuated strain. This is a strain which is characterized by less invasive power than the Mahoney strain, by less antigenic potency, that is, a lesser ability to produce antibody, and this has been mixed in a vaccine that uses proportionately more of the Brunhilde strain in an attempt to make up this deficiency.

I think the Danish interpretation will have to be looked upon one as purely experimental rather than a practical means to an end.

The doses scheduled to be used are experimental in that there is no sound evidence that these doses will be effective. They are inoculating all children so there will be no comparison group to study. They had a recent episode of polio that was surprisingly severe, so there could be expected to be a very high percentage of immunity.

Mr. HESELTON. You say they inoculated all children. Is that all children of a certain age group?

Dr. SHANNON. Yes, sir; but I am not sure of the upper limit. Dr. Francis tells me they are heading for all individuals up to age 45. You have to take Dr. Francis' word for it.

I think the very circumstantiality around the use of this new vaccine in Denmark, the mode of administration, the size of dose, the new strain, the lack of controls and the prior experience with polio some 4 or 5 years hence, unfortunately will not subject or permit subjecting this experience to analysis in a meaningful way. They have sought to take the information developed in this country and put it to a very practical use, introducing such variables as they felt desirable.

As. Dr. Francis points out, they have used the same procedures for inactivation.

To go back to my conviction and that of the Public Health Service, we would agree and emphasize that there is room for improvement in this vaccine, both in measurements of potency and safety measures in addition to substitution of strain. These matters were discussed in a technical report prepared for and presented to Mrs. Hobby by the Public Health Service, dated about June 10.

In short, then, we would hold as the Public Health Service and I as a scientist that we should continue to endorse the manufacture and use of this specific vaccine, subject to the desires of parents and subject to the recommendations of physicians and their local Public Health officers who having been given all the facts either recommend or not recommend that an individual take it.

Dr. PAUL. Thank you Dr. Shannon.

Dr. Francis?

Dr. FRANCIS. Mr. Priest, gentlemen, I too agree that there are advantages to be gained in the substitution of strains which have less virulence for immunization provided they are otherwise effective. But I think that this also introduces several other questions. One of them has been referred to by Dr. Horsfall, that these strains must also be shown to be effective not only under laboratory conditions but they must be suitable for mass production and use and stability under those conditions.

Secondly, the fact that an attenuated strain is used does not mean that it has no risk if there is still active virus in the vaccine. The procedures which would be employed to prevent infection by strains such

as Mahoney should also have to be applied to these other strains, because, while the Mahoney strain if it slips through may produce damage directly, attenuated strains may also change if they are allowed to be present. So it is not simply a matter of relaxing your guard and reducing the requirements for production and safety by saying if they are in there they are active. It makes less difference, because the risk is still there that they may change and become virulent.

Finally, I think that the safety tests and the improved safety testing which has been developed are of such a nature as to give a very high degree of confidence that active virus should not occur. As Dr. Shannon says and I think we would all agree, there is nothing that can give you absolute guaranty under all conditions that no active virus could be present in the preparation.

Finally, the suggestion is that this can all be done in 6 months. If one were to stop the present program, either substituting something which I think has been proved to be effective in the field, it has been proved except for these recent events to be highly safe under those circumstances the suggestion would be that you would really substitute and remove a product which has been safe and effective and substitute for it an unknown, an idea which, at the present time, is still experimental. You would then be substituting a proven product for something which is yet to be proven and which Dr. Sabin thinks might be better, but for which the proof is not yet available and would not be available until it was done.

I think, subsequently, that one may comment upon the fact of the impressions and speeds. I might say I have no vaccine of any kind to sell, nor have we had any role in the production or preparation or the distribution of any form or kind of vaccine. So one still can point up that haze is often of the modern making. One does not go to war slowly any more.

Secondly, if one were to assume that all these things would be done and would be equally effective, then one would be assuming a great deal.

In view of all these considerations, I would certainly be opposed to stopping the present program until the work is developed. I think the suggestions which have been made are there for anyone to work on. There is nothing in the world for hindering anyone for developing different kinds of vaccines and different procedures and there is no hindrance to their being accepted, if the evidence is in that they are satisfactory.

Dr. PAUL. Dr. Francis, would you feel that you have said all you want to say on the substitution of strains in terms of an opinion for or against?

Dr. FRANCIS. On the substitution of strains, I would agree with that provided they are satisfactory. I think one might point out no matter what else he says that the presence of the Mahoney strain and the fact that it did appear in vaccine and produced disease was of itself a significant fact for educational purposes at least. I think, had that not happened, a number of the deficiencies and perhaps inadequacies in the type of reporting that was done on production of material might not have been detected until some other kind of accident showed up.

Dr. PAUL. Thank you, Dr. Francis.

Dr. Hodes?

Dr. HODES. I would like to say about the substitution of strains that this ought to be done provided that it does prove to be satisfactory and that it can be done in a way that has been suggested by Dr. Horsfall and by Dr. Francis.

Regarding the continuation of the program, I feel like this. We cannot say to physicians who are going to inject children, here is a vaccine which has been tested in a way which we think is not quite as good a way as we can test it. I would sum it up very briefly by saying that the program ought to be continued provided the vaccine being injected and to be injected from this point on has been subjected to the safety testing which Dr. Shannon described to us.

I do not know whether this entails a delay or not, so I am not quite certain where I stand on this particular point of continuing.

I would say, to put it positively, that the procedure ought to continue, provided the vaccine available has been tested by the maximum safety testing now available such as Dr. Shannon described.

Dr. PAUL. Thank you.

Would you care to comment?

Dr. SHANNON. I would like to comment on that, yes.

I would like to say, first, that there is no such thing, sir, as maximum safety. The only wholly safe vaccine is a vaccine which is never used. The standard that the committee developed for vaccine to go into production beyond May 26, I believe, is so rigid that it could well be that with a year or so of experience it may be necessary or advisable to modify it. This is pure conjecture. I do not know.

One can calculate and say that the chances of this vaccine containing more than 5 tissue culture units per liter of vaccine is 1 in 100,000 times. That gives an air of precision which is not very meaningful. What it means is taking all the testing procedure that has been done, taking all the vaccine that has been used, this puts a limit of tolerance so far below or so much closer than vaccine that has been utilized before, as to place it in an almost different order of magnitude of safety. There are interim clearance procedures. These are procedures worked out by the best advice we could obtain.

It is their desire to look at each one of these lots as it is submitted under an interim clearance, to request such additional information that will permit each of the series of some five advisers to look at each lot as though it were put under a microscope for any slight deviation of these iterim clearance values.

It is their conviction that this additional examination together with the additional testing procedure brings the safety of these vaccines that are cleared on interim procedures close to and perhaps it may be better than the conventionally produced vaccine under the more rigid requirements as it will be produced in some 6 or 8 months.

I do not believe the committee, as I interpret their views, feels that they are turning out two types of vaccine, a second-class vaccine now and when the interim requirements no longer obtain the other. Certainly it would be impossible to have the type of advice we have on the batch by batch clearance now for a long period of time.

The committee is Dr. Francis, Dr. Salk, Dr. Smadel, Dr. Shope, Dr. Bodian, Dr. Larson, and myself.

I think all of them are taking this with an extraordinary degree of seriousness. I think the batches that are recommended to Dr. Scheele

for release will be recommended after a very careful consideration of each of these very distinguished scientists.

Dr. HODES. I accept Dr. Shannon's explanation. I think we were speaking a little bit at cross-purposes. I think if he feels that if this new procedure is safer than those previously, I would go along with continuing the vaccine. I am sorry I said "maximal safety." What I should have said was "more suitable safeties than previously in use."

The CHAIRMAN. Dr. Hodes, may I ask you this question? I think you have explained it. I recall that on June 16, the Associated Press carried a story out of Chicago to the effect that the American Academy of Pediatrics passed a resolution in which they in effect recommended a discontinuance at the time. I wonder if your position now relates to the more rigid test that is being given, and that is why you feel as you do now, notwithstanding that action of the academy. I assume you are a member of the academy.

Dr. HODES. Yes, sir; I was there. I should say part of this stemmed from a lack of knowledge which Dr. Smadel referred to. The lack of knowledge, the reason for which I won't go into. I cannot speak for the rest of the members of that panel. They may feel quite different. We were not given some of the information that we subsequently had.

The CHAIRMAN. Thank you very much. I thought that should be clear at this point in the record.

Dr. PAUL. I think Dr. Salk was anxious to comment next.

Dr. SALK. Thank you, Dr. Paul.

Since the questions have been broken down in two parts I wish to retain the position that I held yesterday and not enter into the decision. I would like to call attention to a memorandum dated May 20, 1954, entitled "Minimum Requirements, Poliomyelitis Vaccine," which was the first document prepared more than a year ago to guide the manufacturers in anticipation of what might occur a year subsequently. In these minimum requirements there is a paragraph, 1.3, entitled "Strains of Virus," and it reads as follows:

> Strains of poliomyelitis virus used in the production of vaccine are identified by historical records, infectivity tests, and immunological methods. Any strain of each type of virus may be used which produces a vaccine of acceptable potency but preference shall be given to strains of minimum pathogenicity to man if such strains produce a vaccine of acceptable potency.

I call your attention to the fact that this statement with my strong concurrence was introduced into the guide more than a year ago. At that time my concern was with the apparent destructive effect of merthiolate on the potency of the Mahoney strain and it is clear in the course of subsequent tests it was less stable than the type 2 and 3 viruses in the vaccine. As a result of that, we initiated then an intensive program which is still in progress. I merely call your attention to something to which Dr. Francis referred, the length of time it takes to get solid, substantial information.

I won't go into detail now to tell you what really is involved in establishing the relative pathogenicity, the relative potency, the relative stability of a series of viruses to determine whether they are acceptable or not. Lest there be any misunderstanding, I want it to be known that I am in full accord with every desire to make a fully effective vaccine, one that approximates and approaches that which we desire that can be used with a high degree of confidence.

I want to comment on the question of certainties and uncertainties in relation to the safety testing procedures. I want to endorse very strongly the soundness of the program that Dr. Shannon referred to. That is, the present testing program. When the deviations first came to our attention after the Cutter incident, we learned a great deal that we did not know existed before, and as a result of that, this experience has been converted into the wisdom that has provided what I think now is not the uncertainty that Dr. Sabin expressed, that things will get worse or will not change, but things have in fact become better.

Dr. Stanley said that all he can go by are the laboratory data and he looked at the data upon which we too decided that changes had to be made. I want to emphasize that I am interested in more safety and not less safety.

Dr. Francis expressed all of the things that I thought of commenting upon, and that is the importance of being certain that there is no live virus in the vaccine that could conceivably be harmful to man, whether it be Mahoney or any other.

Therefore, I put as a primary consideration, not the substitution of the virus, but the procedures that have already in fact been introduced in the reorganization of the laboratory of biologics control and all of its procedures, in the changes in the testing program.

Now, secondary, and tertiary and still further modifications in their order of importance should be and will be made, I can assure you, with our help and that of many others.

Dr. PAUL. Thank you, Dr. Salk.

In giving the compilations which I have made of the opinions expressed, I want to thank Dr. Stanley for bringing out the point that this is merely an expression of the opinion of this particular group which has been selected on a very broad basis. I hope that by having individual opinions drawn out of us, as it were, that that will help the committee to not only see what the problems have been, but to make their decision.

If my addition is correct, I have counted 11 people voting; 2 have felt that they were not competent, as they said, to vote, in other words, that they were not exactly in this field; 1 has abstained from voting.

Of the vote for the substitution of strains, as far as I can see those voting were unanimous in favor, although several qualified their statement with the proviso that these strains should be shown to be adequate as an immunizing agent. Of those who were in favor of terminating the program at the moment, we have three: Dr. Sabin, Dr. Hammon, Dr. Enders. The vote to continue was eight.

The CHAIRMAN. Thank you, Doctor. I believe Dr. Cornell, executive secretary of the Academy of Science, is in the audience and in furtherance of what I said about the purpose of the panel, I wonder if Dr. Cornell would care to make any statement.

Dr. CORNELL. Thank you very much for the opportunity, Mr. Chairman. I hope I can succeed in clarifying the record rather than in clouding it in any way.

I think the point that Dr. Stanley was making is well taken. That this panel is not in the general nature of Academy committees. It is indeed not an Academy committee. It is a panel invited by your

As Dr. Sabin mentioned the first thing yesterday morning, people in certain of the lower social economic groups or lower hygienic conditions perhaps have a greater resistance or develop infection earlier. It was believed that there might be some difference in this sort that would participate in the decision of a person to want to take part in the vaccination study. On the basis of a survey that we had done last December in these populations, it was clearly shown that the differences between those who did participate and wanted to participate and those who did not wish to participate were sufficiently clear-cut as to warrant the conclusion that they did represent a different population and a population that might be expected to be more resistant.

The vaccinations were carried out, as you know, in April, May, and June. The study period we defined as being the period from 2 weeks after the third inoculation because by that time the presumed response to vaccine would be fully acquired and it also was the time at which blood was taken from a large sample of children in order to measure them for the presence or the response to vaccine.

After that time, there were 1,013 patients that were reported to us as being poliomyelitis. Of these, 428 of these occurred on the placebo areas and 585 occurred in the observed areas.

I would say that the criteria for diagnosis were very carefully reviewed by our advisory group of very eminent physicians and the criteria on which a case was called paralytic poliomyelitis, not poliomyelitis or nonparalyitic poliomyelitis were all established in advance before the analyses were made.

In any case there was a body of cases of this total, of 150 that we considered either not poliomyelitis or very doubtful poliomyelitis. It is interesting to point out, however, that by our criteria 67 percent of the cases were finally classified as paralytic of one grade or another. A number of those were in what you would call the minimal grade paralysis.

When one compared these cases in terms of the vaccinated—and I will speak now primarily of the placebo area, the strict control area but the populations are the same—that there were 270 cases in those areas called paralytic poliomyelitis. Thirty-three of them were in the vaccinated and 115 in the controls. In other words, there is a ratio of approximately 3½ to 1. The rates were 16 per 100,000 and 57 per 100,000 in these paralytic cases. There was no difference observed in the cases that were classified as nonparalytic. There was no difference observed between the vaccinated and the placebo group in those that were called not polio or doubtful polio.

So the difference as detected and as measured essentially is reduced to the paralytic cases of poliomyelitis. In the observed areas the rates were 17 per 100,000 vaccinated and 46 in the controls.

You see that difference is not as great as in the placebo areas and they are essentially two different studies. But the the rates in the vaccinated in each group are essentially the same, 16 and 17 respectively, the difference being in the control.

If one moves to the next step—and here is the problem of diagnosis and certainly of laboratory diagnosis—we move then into the paralytic cases according to whether they had laboratory evidence that they were poliomyelitis. Either virus was recovered, and that was true of the bulk of these cases, or there was a certain proportion whose blood

Congress shall appropriate $35 million in grants-in-aid to the States.

I am sure and unless I have misunderstood some one somewhere, all of this discussion related to the question of continuation of the use of the vaccine rather than to the legislation before the commitee.

Dr. PAUL. That is correct, sir.

The CHAIRMAN. Thank you very much.

Dr. Francis, you may proceed.

Dr. FRANCIS. Because we have discussed certain of these points perhaps the best for me would be to briefly review and give in summary fashion certain of the figures and data that were obtained. You will recall that this was a general program throughout the United States that involved some 214 areas. So it was not homogeneous in geographic distribution.

It was laid out in that fashion with the expectancy that this might catch poliomyelitis wherever it would occur in significant numbers and thus add to the data that could be employed in evaluation.

There were two studies in reality. One, which is that originally described and selected really by the local agencies. That was the "observed area," as we called it, where those children in the second grade were asked if they wished to participate, and those who did wish to participate were vaccinated. They got the vaccine and nothing but vaccine.

The first- and third-grade children were considered the controls. They received no inoculations and therefore we called them the observed controls and these are called the observed study areas.

In those areas there was a total of 1,080,000 children in the first, second and third grade which represented the total population, and approximately 940,000 of those were the study population. These were the studies in which we had greatest confidence. I believe most investigators would feel that way. At least it is done on what you would call strict control scientific basis. All children in the first, second, and third grades of these areas were asked to participate. Those who did wish to participate—and this was made known to them at the time they signed their request for participation—was that they would receive either vaccine or another substance which looked like vaccine and that the idea would be that no one would know who got vaccine or the control material which we speak of as placebo. The placebo or dummy substance was the control inoculation. These populations so far as we can determine are completely homogeneous. That is, they are equal halves of the same population and they do not differ in any significant characteristics.

There were 201,000 approximately that recived vaccine and 201,000 that received the control inoculation. I think this in itself is a remarkable example of the American public's interest in a scientific investigation on a large scale.

The CHAIRMAN. May I interrupt to ask at this point if there were 201,000 who received neither but who were kept under observation?

Dr. FRANCIS. There were 338,000 who received neither, but were kept under observation. I would point out, and this may be as good a time to do it as any, that the people who refused to participate or who said they did not wish to participate we did not consider another group of controls.

As Dr. Sabin mentioned the first thing yesterday morning, people in certain of the lower social economic groups or lower hygienic conditions perhaps have a greater resistance or develop infection earlier. It was believed that there might be some difference in this sort that would participate in the decision of a person to want to take part in the vaccination study. On the basis of a survey that we had done last December in these populations, it was clearly shown that the differences between those who did participate and wanted to participate and those who did not wish to participate were sufficiently clear-cut as to warrant the conclusion that they did represent a different population and a population that might be expected to be more resistant.

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serum was tested which indicated that they had been infected with a given type of poliomyelitis virus, and there was a small number added to this where the virus was not recovered from the patient, but was recovered from members of the family. They were all considered in the "laboratory confirmed" group.

When one takes these data and divides them into the spinal cases or the bulbo spinal cases, there were 8 cases in the vaccinated and 45 in the controls with the spinal, 2 bulbo spinal in the vaccinated and 23 in the controls.

These differences are highly significant. The estimate of effectiveness there, as done by a form of mathematics at which I am not adept, were calculated to be 80 to 90 percent.

In the observed areas, again, the estimate of effectiveness was the same in the spinal cases but was definitely less in the bulbo spinal. Then when we come to the cases that were identified according to the recovery of virus only and specifically the type of virus, it was quite clear that the effect against type 1 was less marked than it appeared to be against the type 2 and 3. This was in keeping with evidence we obtained at the same time from the study in the laboratories of the blood taken from the children before and after vaccination, type 1 effectiveness in a number of lots of vaccine was less than that of type 2 and type 3.

This also is in keeping with the generalization that apparently the type 1 was affected more rapidly by merthiolate than others. At least that appears to be one reason.

So in our subsequent review and attempts to find gaps or errors in these data I think we would still say that although there may be a few minor changes because of data that have been obtained later by reports from laboratories, that these favorable results in effect still stand.

Several questions have been asked why the nonparalytics did not show a difference. We have no simple answer to that. There are two possibilities. One is that you have enough mixture of polio and not polio together that that would mean a difference. On the other hand, it may also indicate that the vaccine does not prevent infection alone, although it may limit the severity of the disease.

The second question was about the 6-year-old children because in those figures they were shown to be less influenced than certain of the other age groups.

Mr. SPRINGER. I would like to ask, since Dr. Francis has done such a wonderful job of interpreting the figures on page 25, I wonder if he has completed his statement? If he has not I think he ought to have an opportunity to finish it because I think this has a great deal of bearing on 1955.

Dr. FRANCIS. Which data?

Mr. SPRINGER. Did you complete your statement as to your figures on page 25? Had you completed your statement?

Dr. FRANCIS. No. I was simply hitting the high points which is about all anyone could expect to do here.

Mr. SPRINGER. That is all, Mr. Chairman.

The CHAIRMAN. Dr. Paul, was it your purpose to have a panel discussion of Dr. Francis' report before this committee questions?

Dr. PAUL. I would be happy to ask if anybody would want to comment on that briefly.

Dr. SABIN. Yes, sir. I would like to ask Dr. Francis some questions and make a comment or two simply to give him an opportunity to dilate on this. The first question has to do with nonparalytic poliomyelitis. When I said yesterday morning that 35,000 to 50,000 cases roughly have been reported every year during the past 5 years, about half of those are so-called nonparalytic.

Now, in the interpretation of nonparalytic it means that the central nervous system has been invaded by the virus. If the vaccine is supposed to prevent invasion of the nervous system by the virus, we are faced with a very difficult question which yet remains to be answered: Why was there no significant effect in the nonparalytic cases even in those in which polio virus had been demonstrated to be active?

The second question: If we are going to base our actions in the future on demonstrated effectiveness, the question remains: Why is it that in 6-year-old children in 1954 Dr. Francis concluded there was no significant effect of the vaccine? Are we for the moment, until new data becomes available, to assume that children that are 6 years of age or younger are not significantly protected by the vaccine? I am not unaware of the fact that vaccine produced in 1955 and 1956 may be a great deal better, but let us remember that that still remains to be proved.

On the basis of existing data we cannot flatly state that children that are 6 years of age or under have been or can be significantly protected by the vaccine. They may be, I think they will be, but we do not have the evidence now.

No. 3, I would like Dr. Francis to interpret for me the summary of his data on page 50 of his report under the heading of "Percentage effectiveness" in which the data are summarized and mathematically analyzed as to percentage effectiveness, and we are given two figures. Estimate and lower limit.

The variations are something like this: For type I, which after all causes 80 percent of the paralysis in this country, estimated in one group is 68 percent; lower limit is 41. In another group, it is 62 and 33.

For type II, estimated 100 percent; lower limit 33 percent. In the other group of type II, estimated 80 percent; lower limit 33 percent.

I would appreciate very much to have Dr. Francis' comments. Before I finish, I feel a little bit like a dog to ask these questions because there is not a colleague of Dr. Francis who is not greatly impressed and deeply grateful for the stupendous amount of work that he and his associates have done. Perhaps never in history before in analytical epidemology has anyone done a job such as he has done.

I am asking these questions in all good faith in attempting to get more understanding.

Dr. FRANCIS. Thank you for your very kind remarks. I am glad to have these questions raised because they are questions with which we have been confronted and at the same time I hope he would have asked another one which he didn't but I will answer it, too, if I can.

The first one, why the vaccine did not have an influence in the nonparalytics, all we can say is that these are the figures based on the way the cases fell out. They were characterized as nonparalytic before any knowledge was had as to whether they were vaccinated or controls or who they were.

I suggested briefly that our simplest suggestions have been either there is just enough mixup of all sorts of things in there to obscure any effect that might have been present, or secondly, that it would indicate that the vaccine of itself does not prevent the milder infection but may prevent the extension into the central nervous system of the paralytic disease.

The second question about the 6-year-old was about what I was to take off on at about the time the bell rang. The data there we expressed in one sentence as pointing out that there was not a significant difference between the vaccinated and the controls in the placebo areas in the 6-year-old age group. We even went so far as to say thus there appears to be a progressive increase in the protective effect as age increases.

Last Friday we again had our advisory committee meeting in Ann Arbor. We, too, have advisory committees. They discussed at great length this entire question. We were taken to task rather seriously for even using what we thought was conservative wording "thus there appears to be progressive increase". The statistical data indicate that we are probably wrong in that statement, that there is no significant difference between the rates in the 7-year-olds and the 8-year-olds. But there is no doubt that the 6-year-olds deviate very sharply from what would be expected if the vaccine were having full effect.

This is taking the total cases. When one breaks those down again, however, in terms of the virus positive cases, it shows up with our present figures—and part of these are in the report on page 41—that there were 4 type I cases in the controls and 4 in the vaccinated in the 6-year-olds. There is 1 type I in the control and 5 type III's in the control. There is now an additional type II in there, so it would be two type II cases.

If one then considers this, you have seven type II and type III cases in the controls and none in the vaccinated; whereas there would be no difference between the type I. Taking the overall figure there, you would have 11 and 4, which is different, of course, from the other figure of 16 and 23. These again are the same procedures that were followed before.

We have other analyses of these persons to see whether they were different serologically from the mass of other cases. We also should point out that we are confronted—and this again was one of our problems—by the fact that 3 of these were from Massachusetts where most all cases that were reported as polio were another type of disease and Dr. Enders and his associates have worked at great length this summer and fall to try to find out what they were. At least they were associated with a disease that had resemblance to polio clinically, but it was not a disease that was really associated with the usual types of poliomyelitis virus.

We also had 3 cases from central New York State where "orphan viruses" were recovered and this was also an area in which this finding was very highly prevalent.

In the controls we also had 4 of these from Massachusetts and 4 from central New York. So that may again eliminate a certain number of these cases if they are considered not to be poliomyelitis.

So if we were to take the various positive information again we would say that there was a distinct difference between the vaccinated placebos but not against type I virus.

I think that is as far as we could go with that.

The CHAIRMAN. I am sorry for this interruption, but Mr. Heselton, of Massachusetts, will have to leave shortly. We welcomed him back to the committee a few days ago after a rather long period of illness and we are happy to have him here. He has to leave and he has one or two brief questions he wanted to ask. I am going to ask if you will indulge at this moment and allow Mr. Heselton to ask these questions and then proceed with the answer by Dr. Francis to your questions, Dr. Sabin.

Mr. Heselton?

Hr. HESELTON. I appreciate very much this consideration, Mr. Chairman. There are two questions I want answered for the record. One in the nature of a request. Can there be furnished copies of this particular report, Doctor, to individual members of the committee?

Dr. FRANCIS. Sir, I thought they had already been provided earlier.

Hr. HESELTON. Possibly they had. The clerk indicates not.

Dr. Francis, can they be furnished to us?

Dr. FRANCIS. Yes, they can be. Dr. Shannon or someone from NIH can do it.

Mr. HESELTON. I do not know whether it is a fair question to you. I do not know who made the statement, but my understanding was that in the field test of 1954 the three vaccinations were completed by the end of June. Is that correct?

Dr. FRANCIS. No. Most of them were finished by the middle of June. There were a few areas that went later. In Canada, of course, they went later.

Mr. HESELTON. If I understand correctly the testimony of some other individual, it has been determined that it is wise to hold the third vaccination for a period of 7 months after the second vaccination. Has that been a new development, and if so how does it come about?

Dr. FRANCIS. There again I am not responsible for either of those developments or decision.

The decision to proceed with the 3 vaccinations within the 5-week period last year was made by the advisory committee of the National Foundation for Infantile Paralysis of which Dr. Rivers was chairman. The decision to delay the third inoculation until the autumn in the current year was also made at their recommendation on the basis of data that Dr. Salk had presented, indicating that after a longer interval the third dose did a great deal more than if it was given a short time later. In a short time it added very little more to the effect of the second dose. I think that is correct, Dr. Rivers.

Dr. RIVERS. I think Dr. Salk should answer the question because the decision that the vaccine advisory committee of the NFIP made was based on the data given by Dr. Salk and I think he should present it.

Dr. SALK. Mr. Heselton, I will make available to you a copy of the report upon which this decision was based. There is graphic presentation indicating the antibody response to the first dose, the second dose, and when the third dose is given at a short interval I think you may be able to see that there was no further rise. On the other hand when an interval was allowed to lapse of some 7 months or longer the effect is shown here, as such. I think you can see on this chart.

The first effect, and the second dose, and when the third dose was given 7 months later you see the very sharp rise in antibody. There was a gradual decline over a year. The total time from beginning to end was a year and a half.

And you see another dose here which produced an effect of this sort. We have observations on some children who have been observed for a period of 2½ years and you can see that this long interval produces this very sharp effect.

Mr. HESELTON. Thank you, gentlemen, and members of the committee.

The CHAIRMAN. The bells have rung for the rollcall. That is one question that we committee members have to face. We had hoped to conclude by noon. Apparently we have not been able to do so.

Would it be possible to have at least a short session during the afternoon, Dr. Paul?

Dr. PAUL. Yes, sir. I should hope that we might conclude in an hour.

The CHAIRMAN. I realize and I know the committee realizes the sacrifice that all of you gentlemen have made to come and give us this assistance. I do not think if I were a master of rhetoric I can ever express our appreciation for what you have done.

I had hoped to be able to conclude by noon today so that you may go to the many duties that are calling you in many different spots. Since we have not been able to, and with the understanding among all of us that we shall attempt to do so within an hour after we reconvene, the committee will stand adjourned until 2 o'clock.

(Whereupon, at 12:05 p. m. the hearing was recessed to reconvene at 2 p. m. the same day.)

AFTER RECESS

(The hearing was resumed at 2 p. m.)

The CHAIRMAN. The committee will come to order.

Mr. Springer had a few questions to direct to Dr. Francis before we proceed, and may the Chair assure all of you that we will make every possible effort to clear the panel within an hour because I know that all of you have pressing engagements.

Mr. Springer is recognized.

Mr. SPRINGER. Dr. Francis, would you turn to page 25 of your summary report of April 12, 1955? I am referring now for the record to table 2 (b), the summary of study cases by diagnostic class and vaccination status, rate per hundred thousand. Going to line 3, vaccinated, the study population was 2,745. Your number of paralytics was 33, and the rate was 16. Now going to the second line, you had the same number under study and the number of paralytics was 115, or 3½ times, and your rate was 57.

This is the question, Dr. Francis: Do you think this is generally indicative of the effectiveness of this vaccine in the trial run studies of 1954?

Dr. FRANCIS. In the total cases there, that is taken to be the total paralytic group in the placebo area. That is 33 and 115. In the table on page 50 that again is referred to in the third line in the left-hand column of figures.

Mr. SPRINGER. Would you read those figures, Doctor?

Dr. FRANCIS. There are again 33 cases in the vaccinated and 115 in the controls, listed as all paralytic. That is in table 10, on page 50.

The CHAIRMAN. While he is checking on that, may I inquire if the control includes those who receive placebo and those who received no shot at all?

Dr. FRANCIS. No, sir, the placeboes are the controls, and the others are in different populations. There the significance of the differences between those occurrences is within the range that this could occur once in less than 1,000 times as being due to chance.

Mr. SPRINGER. Going again to page 25 of your report, to the observed areas, the second line, "control," and then going to the paralytic number, 330, the rate 46, again comparing this with the line before of vaccinated, there is a startling difference there; is there not?

Dr. FRANCIS. That is the rate of 17 and the rate of 46. There again the estimate of the significance there is that this would be due to chance in less than a thousand times. In the estimate of effectiveness in the placebo areas, that total paralytic estimate was approximately 70 percent effective. In the figures for the observed areas, it calculates at around 62 percent.

Mr. SPRINGER. But the overall picture is what I am trying to get, that there was a startling difference in the number of paralytic cases between those which were vaccinated and those which were not vaccinated.

Dr. FRANCIS. And that is the whole basis for estimating the effect.

Mr. SPRINGER. Now, I want to go back, if I may to line 3, again, on page 25, to what is called Vaccinated. There were 200,745, Dr. Francis, of which 33 were paralytic. I run that figure of 33 as against 200,745, and I come to the figures of 6,080. That means that 1 out of every 6,080 inoculated in 1954 trial run later had paralytic polio. Does that bear out?

Dr. FRANCIS. I would think so. I would be 16 per 100,000 or 1 to 6,000.

Mr. SPRINGER. Now coming back to the figures for 1955, I want to include in that the Cutter figures. Those are 4,843,426. There were 131 cases, including the nonparalytic cases. That comes out at a ratio of about 1 in 40,000. Does that come out?

Dr. FRANCIS. I have these figures, but I think there is one difference. These rates (in my report) that we are talking of covered the period from June 15 approximately until December 31. Yours are for a limited period, a much shorter period, so that the time factor would not be in proportion, or would not be the same. You would have to multiply it by six.

Mr. SPRINGER. But the number of cases of instance was 1 in about 40,000 of those inoculated, was it not, in this year, of 1955. Now, Doctor, going back to the end of the trial run in 1954, you must have figured out that the chances of getting polio after inoculation was roughly 1 in 6,080 cases. Now, were you willing——

Dr. FRANCIS. You mean after inoculation, or after completion of vaccination?

Mr. SPRINGER. After completion of vaccination, I stand corrected on that point.

After completion of vaccination, your chances of getting polio was 1 in roughly 6,000; is that correct?

Dr. FRANCIS. Paralytic, yes.

Mr. SPRINGER. Who then recommended this program to be continued in 1955, who was responsible for making that recommendation?

Dr. FRANCIS. I would suggest that one of the first comments on that might come from Dr. Rivers again.

Dr. RIVERS. Sir, the advisory vaccine committee of the National Foundation had nothing to do with what happened in 1955. We had something to do with what happened in 1954. What happened in 1955, sir, was that Mr. Basil O'Connor of the National Foundation said that he would buy enough vaccine to vaccinate 9 million children if the program went on. I do not know who advised the National Institute of Health to go ahead.

Mr. SPRINGER. You do not know who the committee was that made up that evaluation and that recommendation?

Dr. RIVERS. I do not, sir.

Mr. SPRINGER. I would like to call on Dr. Shannon.

Dr. SHANNON. I think that I probably recall them all, but if I have forgotten anybody perhaps you could recall them. From the National Institutes of Health was Dr. Haus, Director of the Microbiological Institute. This is a recommendation for licensing, sir. Dr. Workman was chief of the laboratory of biological control, and Dr. Habel, Dr. Bell of the same laboratory, and I believe there was a fifth one, and I am not sure. Maybe it will come to me.

Dr. SALK. Was it Dr. Murray or Dr. Price?

Dr. SHANNON. Dr. Price was not but Dr. Murray was.

Outside of those who participated in the deliberations was Dr. Sabin, Dr. Paul, Dr. Smadel, Dr. Turner, and Dr. Hammon.

Dr. SALK. Dr. Shaughnessy was also.

Dr. SHANNON. Yes, from Chicago, he was on the group. This group was called together after the presentation of Dr. Francis' data.

Mr. SPRINGER. What data?

Dr. SHANNON. Dr. Francis' data, in Ann Arbor, and the group had the background of the proposal and a great deal of detailed information on the planning of the field study and a great deal of detailed information prior to the report. And on the basis of the report they recommended, that is Dr. Workman recommended and Dr. Smadel and Dr. Scheele, that a product license be given to cover poliomyelitis vaccine as then described.

Mr. SPRINGER. Now, Dr. Shannon, just one further question: At the time they recommended this, they had before them Dr. Francis' report?

Dr. SHANNON. Yes, sir.

Mr. SPRINGER. Which showed in effect that your chance of getting polio even after a vaccination was roughtly 1 in 6,000?

Dr. SHANNON. Yes, sir.

Mr. SPRINGER. Now I want to ask Dr. Francis a question.

Dr. Francis, actually this program based upon these figures which we have already had of an incidence rate that came after vacccination in 1955 in spite of all of that, this program has been over six times as successful as it was in 1954; hasn't it?

Dr. FRANCIS. I do not see how you figure that out.

Mr. SPRINGER. Let me ask you this question: There is no question, is there, that your chance of obtaining it in 1954 according to your study is 1 in 6,000, roughly?

Dr. FRANCIS. That is the people who had the vaccination, but that was with the incidence at that time.

Mr. SPRINGER. This year you have had 131 cases, as of June 15, and that includes paralytic and nonparalytic.

Dr. SABIN. The season has not started yet.

Mr. SPRINGER. I am talking about what has been done thus far. You had 131 cases reported, as of June 15, 1955.

The CHAIRMAN. Do you refer to paralytic cases?

Mr. SPRINGER. I am referring to both. There were 92 paralytic cases and 39 nonparalytic.

Dr. FRANCIS. May I ask, would you clarify for me in these numbers, these 4,843,428 are what?

Mr. SPRINGER. They are the number of vaccinated thus far.

Dr. FRANCIS. And the 131 cases come from where?

Mr. SPRINGER. Those are the ones that have come out of these vaccinations that have been reported.

Dr. FRANCIS. I see.

Mr. SPRINGER. I believe these figures are correct, and I will stand corrected, but I think that I have the correct figures. As of June 15 there were 131 cases.

Dr. FRANCIS. Since when?

Mr. SPRINGER. Since this program started.

Now, with 4,843,426 vaccinations, the way that comes out to me is 1 in 40 000 thus far. Now, I will concede that Dr. Sabin has raised a point that someone still might get polio later on, and I am talking about now as of June 22, 1955.

Dr. FRANCIS. As of June 22, last year, we had 129 cases in the total population, total study population, and not just in the vaccinated, so that the numbers here if these are correct would be just about the same as of this time a year ago, from the 1st of May until about the middle of June. We had 129 cases, which would make this just about the same. Now what happens after that is a different story.

Mr. SPRINGER. Are you talking about the 129 cases out of the 500,000 that was inoculated, Doctor?

Dr. FRANCIS. I am talking about 129 cases that occurred in persons from the time the first inoculations were begun until 2 weeks after the third inoculation was completed. There was 129 cases and that actually brought us to the date of June 20, which would be just about the same period that you are talking about.

Mr. SPRINGER. Did those include those nonvaccinated as well as others?

Dr. FRANCIS. Yes, sir.

Mr. SPRINGER. That would hardly apply to this.

Dr. FRANCIS. You have a population that is not divided up our way.

Mr. SPRINGER. I can understand there might be a problem of difference of population, but still coming back to the question of the people inoculated and the time which has intervened since the inoculation, the percentage of people who are having polio is considerably less, is it not, in this group?

Dr. FRANCIS. Yes; but if you will multiply that by 6 again, which would give you 6 months instead of 6 weeks, or instead of 1 month, you would end up with 6 times 6, which would be 36,000, as opposed to 40,000 which you are calculating now.

Mr. SPRINGER. Then I would have to back up on that line of questioning, if what you say is true, and I think you possibly have a point. It would bring you back to six times that much polio occurring, and you would be back roughly to the same figures that you had last year?

Dr. FRANCIS. That is right, sir.

Mr. SPRINGER. I think that that is a fair statement.

Dr. FRANCIS. In other words, your notion is that you would be estimating the effect at this rate of being the same.

Mr. SPRINGER. The same as it was last year.

Dr. FRANCIS. Yes.

Mr. SPRINGER. Mr. Chairman, I believe that is all.

The CHAIRMAN. Are there further questions of Dr. Francis?

Mr. DEROUIAN. Dr. Francis, just so that we can wrap up this subject in a little nugget for the American people to determine, you are an expert and you have done a lot of work with polio patients. In your opinion, as of today, do you think that there is more risk of a person getting paralytic polio if he is vaccinated or if he is not vaccinated?

Dr. FRANCIS. Do you mean in generalization, now?

Mr. DEROUNIAN. Generally. I think that you can make a general statement based upon the experience you have had with patients.

Dr. FRANCIS. One would automatically on that basis assume and support the assumption that there would be less chance he would get paralytic polio if he received a proper vaccine than if he did not.

Mr. DEROUNIAN. Is the degree of the chance less just by a shade or is it tremendously greater if he is not vaccinated?

Dr. FRANCIS. You use the word "shade" and the word "tremendous." I would say if we still talk in the rate of 70 to 80 percent effectiveness, it means that he would have a 20-percent chance as opposed to a 100-percent chance in the controls. That is with these data you have reduced the probability to one-fifth.

Mr. DEROUNIAN. So that overwhelmingly he would have a greater chance of not getting polio if he were vaccinated today?

Dr. FRANCIS. On paralytic polio; yes.

Mr. DEROUNIAN. This in spite of the Cutter experience and everything else that we have had up to date, based upon the experience you have had in all of these cases.

Dr. FRANCIS. With proper vaccine; yes.

Mr. DEROUNIAN. Would you consider the vaccine safe, as to today; or not?

Dr. FRANCIS. Is that a sequitor? It is to say that because of these figures last year, is the vaccine safe today?

Mr. DEROUNIAN. Assuming all other conditions the same.

Dr. FRANCIS. Under the present conditions being established for its control and testing and supervision, the vaccine that should be provided from here on would have a high degree of safety.

Mr. DEROUNIAN. The reason for my questions is that we are going to be called upon to make recommendations for appropriations on this bill. Certainly, we do not want to expend moneys to purchase a drug that is ineffective. We want to know whether this vaccine is effective. I am convinced that it is. But some of the panel differ, and I wanted to pinpoint the opinion of the other experts on the matter.

Dr. FRANCIS. That would be my opinion.

Mr. DEROUNIAN. Thank you.

The CHAIRMAN. In line with the question Mr. Derounian just asked, I have one question.

Dr. Sabin, this morning I understood you to say, in effect, that the issue here is somewhat of a moral one rather than a scientific one. If I properly understood you, the moral issue presented was whether parents with their eyes open and with all of the facts would decide to take a small chance that their child might contract polio from the vaccination as against an infinitely greater chance, according to the record up to date, that the child might be protected against polio because of the vaccination.

Was that your statement, generally, or the substance of what you said?

Dr. SABIN. It was largely that.

The CHAIRMAN. I think that is the question as Mr. Derounian has pointed out. It is a question that the committee will necessarily consider and consider most carefully in recommending to the Congress whether the Congress shall appropriate money in view of that sort of a moral issue. It is not an easy question to decide.

Now, I might add, before going further, that this panel has been extremely helpful, and I think it is helping the committee to get a great deal of information that will somewhat lighten the load of our decision.

If there are no further questions of Dr. Francis, Dr. Paul, you may proceed with your panel.

Dr. PAUL. Mr. Priest, we have only two more items on our agenda.

Dr. SABIN. Excuse the interruption, please, Mr. Chairman, but there was one question that Dr. Francis still had to answer, and it was put into the record. He did not answer it at the conclusion of the last session. Since he, I think, would like to answer that question, I would also like to refer to the table which Mr. Springer used so much a minute ago. That is table 2 (b), on page 25. That deals with the statistics in the observed areas, where some children were vaccinated and others merely had to be observed. They were, therefore, the controls and others were second grade, not inoculated, and we find the following figures under "Paralytic": Among the vaccinated the attack rate, paralytic attack rate was 17 per 100,000. Among the controls it was 46 per 100,000.

But then when we move on down to the second grade, not inoculated and there were 123,000 of those, the attack rate was 35 per 100,000, so that the difference between the vaccinated and the second grade, not inoculated was 17 to 35 rather than 17 to 46.

Do you think that social-group differences also operated in this situation? I hope you do not mind answering this along with the other question, Dr. Francis.

Dr. FRANCIS. This was one of the third questions I was going to answer, if Dr. Sabin had not asked it this morning.

The first one, I must say that Dr. Sabin asked what these figures on table 10, on page 50 means, which referred to the lower limit of the estimate of effectiveness. If Dr. Sabin would care to turn to page 62 of the appendix, the full mathematical equation is presented there as a basis for computing the confidence limit, the lower limits of effectiveness.

Dr. SABIN. Would you translate it for me? I do not understand that.

Dr. FRANCIS. Frankly, I do not either.

That is on page 62 of the appendix. The thing that it does mean, however, is that when the significance levels are high, and you then turn around and calculate the figures that we have as the estimate of effectiveness, they are actually the figures that apply to these data. If you reduced those estimates of effectiveness so that instead of being 1 in 1,000, they were 1 in 20; then instead of being 80 percent effective, or 82 percent effective, there under the laboratory confirmed spinal cases, you might have at that level of confidence a limit of effectiveness of only 65 percent.

In other words, this is a calculation of what is the lowest limit that you could calculate that these figures as they stand might be if the limit of significance were smaller.

I am not a high-grade mathematician so that beyond the point of that general clarification I could not interpret the rest of the formula.

The CHAIRMAN. While you are still on that subject—did that answer your question, Dr. Sabin?

Dr. SABIN. Yes; thank you.

The CHAIRMAN. While you are still on that subject, and this may have a very logical explanation, in studying some of the tables of the various places where the field trials were held, I came across some figures, and I do not have them before me because I do not have that table, that raised a question in my mind. I say it may have a very logical explanation. But in several counties where figures were given on the three groups, those who received vaccine, and those who received placebo, and the observed group, it appeared in a number of instances, or several instances, that there was a higher incidence among those who received the placebo than those who received no inoculation at all. I noticed that in a few counties, and I wondered what the explanation if any is for that development?

Dr. FRANCIS. I think that that is a part of the same question Dr. Sabin was asking me about.

The CHAIRMAN. I thought it was closely related to that.

Dr. FRANCIS. It is the same thing. Actually, it was not only in some of the counties but in general that was true, that the incidence was higher in the placebo population than it was in the noninoculated members of the population, or the ones we did not count controls.

The point I would like to emphasize from here on, and I mentioned it briefly this moring, is that the placebos are controls and the others are not. We do not take the others then as the standard of reference, but we take the placebos. Now the question still comes up as to why they are higher.

I mentioned the survey that had been made in terms of the characteristics of the population that participated or did not wish to participate and that is referred to in the report. It is our belief, on the basis of these considerations that the differences between the yeses and the noes is sufficiently great to stamp them as different populations with different social and economic and educational and health attitudes from the ones that said yes. I think the data are quite clear on that score.

To go back again to what Dr. Sabin was saying yesterday, that the information is available at present in a general way, to suggest still that people of the higher economic levels have less immunity than the others, and the noes represent then a more resistant population.

Now, there are some interesting arithmetical features about these. The controls in the observed areas do not have as high a rate as the controls in the placebo areas. The placebo area controls were yeses, and they were all yeses and they are the same population as the ones that got vaccine. The controls in the observed areas are both yeses and noes, the ones that might have volunteered if they had been going to get vaccine, and also the ones who would not have volunteered if the vaccine was offered them. This was just in the nature of that kind of a study.

Now the ones who were not inoculated in the second grade again are noes that are comparable to the noes in the placebo area, presumably.

You will notice that the rates in those two groups are the same. In other words, the rates in the noes in the observed areas and of the noes in the placebo areas are the same; it is 35 and 36.

The rates in the observed areas of 46, as opposed to 57 in the controls of the placebo area; that is halfway between the yeses and the noes.

If one pools, as he would not, all of the yeses and the noes in the controls, in other words, you pool the placebos and the not inoculated in the one area and the controls and the second grade, not inoculated in the other areas, the rates are exactly the same. So that I think just the ordinary arithmetical fallout suggests that they are quite comparable, except they are not the same populations at all steps.

The CHAIRMAN. Thank you very much.

I imagine that is the logical answer as could be had on that subject.

Dr. Paul, would you proceed?

Dr. PAUL. I think, if there is no further discussion on this point, we can go to the next item. That will be given by Dr. Rivers.

Dr. SALK. Dr Paul, did you want me to say anything about the persistence vaccination effect, or not? Some questions had been raised. It is quite agreeable to me not to say anything further.

Dr. PAUL. Dr. Rivers is going to talk about the reinoculation.

All right, Dr. Salk, if you want to proceed.

Dr. SALK. I will keep it brief.

The question has been raised as to whether or not reinoculations will be required year after year.

The CHAIRMAN. I was planning to ask that question of someone before we concluded, and I am very happy that you will make some comment because it is a question most frequently asked members of this committee by other Members of the House. That is, How often will inoculations be necessary.

Dr. SALK. Well, I think that following Dr. Francis' remarks, it is pertinent to point out that the field study of last year was conducted under circumstances where primary immunization had been given with vaccines that varied in potency. That has already been referred to many times.

By "primary immunization," I mean the effect that can be induced by one or more inoculations given within a short period of time. It has been observed that when a third dose of vaccine, let us say, is administered a short time after the second, it provides little additional benefit as I pointed out this morning, and I will provide some additional information for the record.

When, however, an interval of 7 months or longer is allowed to elapse between the first or primary inoculation and the secondary

or booster, then the character of the antibody response changes very markedly, so that it then resembles the type of response that one observes following the infection itself.

Therefore, I should say the evidence points to the ability to simulate the antibody response to infection by the use of three doses of vaccine spaced as has been recommended. The observations following such a course of immunization indicate that the degree of antibody persistence is such that there still remains at the end of 1 year after the booster a very substantial amount of antibody, and the rate of decline of that is such as to suggest the likelihood that the antibody will remain for a number of years, the full length of time of which still remains to be established.

I must say in direct answer to the question, how long will antibody persist, that of course I cannot say now how long it will persist in the future. But merely from an observation of the trends of experiments that are continuing and observations over a period of 2½ years, I can say that the trend of the persistence is such that reinoculations will not be required every year, and I can say, furthermore, that the likelihood is that the pattern that might have to be followed may well be like the pattern that is followed in the use of other immunizing agents such as for diphtheria, where the immunization is done in the first year of life, perhaps a booster inoculation the second year and, as now is done, there is another inoculation subsequently, before school; but whether or not these subsequent inoculations will be necessary, one or more, is something that we will be able to tell several years hence.

Mr. HAYWORTH. If the inoculations have to be repeated, and if the disease has an increasing likelihood of severity in older ages, it would make it all the more important for the population to continue to get those inoculations, would it not?

Dr. SALK. It would, and this is a bridge that we will cross when we come to it, in the sense that we have under study our own groups that are now some 2 years in advance of the children, or 3 years in advance of the children who are being inoculated this year. We should be able to anticipate those things.

Needless to say, it is an important aspect of the problem because any practical immunizing agent should be one that preferably does not require attention periodically. Rather than go into the esoteric immunology of the problem, I can really say that our own interpretation of the facts that are at our disposal suggests that we have been able to simulate the immunological effects that are produced by infection by the use of the kill virus vaccine. Does that answer your questions?

Mr. HAYWORTH. Yes. Will the chart which Dr. Salk just showed us be in the record?

Dr. SALK. I will make that available.

The CHAIRMAN. We will make that a part of the record.

(Information referred to was placed in the committee files.)

Mr. HAYWORTH. I do not know to whom this should be addressed, Dr. Paul, but I did not succeed in getting an answer because I did not make it plain enough 2 days ago or yesterday in regard to the cost, identifying whether or not a person is immunized.

What I am trying to get at is this: If it is as cheap to decide whether or not the level of antibody is sufficiently high as it is to im-

munize, I can see in many cases, especially with adult population, we might as well find out whether or not a person already is immunized.

Dr. PAUL. I think that we have to measure the cost not so much in money as in the available personnel to make such tests, Mr. Hayworth. I imagine that within a few years—and Dr. Salk can speak confidently about this, I believe—that there may be simple tests available for many people. But I do not believe that at the moment the enormous numbers of so-called tests for resistance could be readily done when you think of the millions and millions of people on which they would have to be done. Perhaps Dr. Salk could comment on that.

Dr. SALK. We have attempted to employ a simple test involving a drop of blood from the finger, and in a matter of, I think it was 2 weeks, we were able to survey 15,000 children.

It gave us a great deal of information quickly, but when we estimated the cost of this operation in terms of your suggestions and the personnel involved and all of the rest, a year or 2 from now it would have been far less expensive to vaccinate than to perform this particular test. The experience, as you well know, with the Schick test for diphtheria and other such tests have indicated that it is usually easier to give another dose of vaccine than it is to test.

However, I might say that we have every intention of following for a number of years these 15,000 children to see to what extent reinoculation may be necessary and we will follow these children with the necessary blood tests and try to predict what is good for the rest of the population.

Mr. HAYWORTH. There is a possibility then that a relatively inexpensive test can be derived for getting the level of antibodies for this disease?

Dr. SALK. Again I would repeat what Dr. Paul said; that the cost would not be the factor, but the number of people that would be involved in terms of the return from the viewpoint of the information that it would give you.

Mr. HAYWORTH. You mean the number of people involved in doing the test?

Dr. SALK. Yes, in doing the test. At our present state of knowledge, I see no practical test like the Schick test for diphtheria for testing adequacy of immunization. Adequacy of immunization can be determined by means of a blood test, that at the moment is a little too costly or a little too cumbersome to be applied to determine who should get the rationed vaccine at this time.

The CHAIRMAN. If there are no further questions, you may proceed, Dr. Paul.

Dr. PAUL. We can move along promptly to our discussion.

Dr. SABIN. I would like to comment on Dr. Salk's reply to Mr. Priest. It is quite possible with reference to the question of how often will reinoculation be necessary that all the predictions that Dr. Salk has made may turn out to be true. On the other hand, the best description of that is a phrase which I like to borrow from Dr. Smadel, and he calls a thing like that "a guesstimate."

I think the honest answer at the present time as to whether or not and how often, even, reinoculations will be necessary is we do not know; and we shall not be able to learn it in the laboratory, we shall only be able to learn it by the continued operation of a unit such as the

Public Health Service now set up, the so-called Poliomyelitis Surveillance Unit, to keep track of what actually goes on in the field, not to a small number of children in the laboratory.

The best we have now is 60 percent, and at a lower limit of confidence perhaps 40 percent of type I, the most important type. We as yet know nothing about what is required for the younger age groups. Therefore, to guide ourselves, I think the best and the most honest answer is that we do not know. We will have to find it out in future years.

The CHAIRMAN. Dr. Sabin, your remarks at that point underscore a statement you made before this committee in 1953. I cannot quote you exactly, but I recall the substance of a statement you made at that time to the effect that once we have developed a poliomyelitis vaccine and have inoculated large numbers of the population with such a vaccine, many of our problems begin at that point. I recall your statement at that time in connection with what you have just said.

Mr. SPRINGER. I think Dr. Salk wanted a rebuttal there, Mr. Chairman.

Dr. SALK. I wanted to agree with Dr. Sabin.

The CHAIRMAN. Very well.

Dr. SALK. And to say that I was commmenting on studies of antibody, and not performance in the field. You must remember, of course, that I am making an assumption and that there is an identity between the presence of antibody and the presence of immunity.

I quite agree with Dr. Sabin's reference to the performance of the vaccine, particularly for the type I, during last year, that there was an association of poor antibody response, and all of this has given greater confidence to the feeling that we should be able to make predictions on the basis of measurements in the laboratory; to expect that we will have to continue to do field studies year after year after year is a rather weighty and gruesome anticipation.

Dr. PAUL. Before our discussion gets too general again, let us recall that we had words of guidance from Mr. Priest this morning to try to stick to the problem that is confronting the committee. Will there be further discussion? If not, Dr. Rivers, perhaps you can proceed with the next item, the point being that there has been much discussion in the newspapers as to whether this material should be given during the summer or during epidemic times, and there may be a difference. But he will tell us about it.

Dr. RIVERS. This is a subject that has caused a great deal of discussion and there is some differences of opinion concerning it. You have probably seen in the newspapers the word "provocation." What I am going to discuss is provocation. That means when a child is infected with poliomyelitis and is in a stage where he is carrying the virus, probably in the blood, will an injection of whooping cough vaccine, or will an injection of penicillin at this time produce in that child a paralysis, particularly in the arm in which the injection was made, that would not have occurred in the child if the injection hadn't been made.

Up until last year this question of provocation had nothing to do with poliomyelitis vaccine. It had to do with the use of other vaccines, vaccines against diphtheria, whooping cough, tetanus, and so forth.

Now the question comes: Will we give injections of poliomyelitis vaccine in the summer in order to prevent poliomyelitis? In other words, the problem is somewhat different from the one that existed before. Previously we were giving substances that had no protective effects against polio. Now we are considering the injection of a vaccine that will protect, not 100 percent, but will protect in a considerable number of instances against the disease.

There have been a number of meetings held in the last 2 or 3 years about this. The last one that was held was held in New York on the 18th of June and it was a large group of people representing many organizations and I would just like to mention the organizations represented:

The Academy of General Practice, the American Academy of Pediatrics, the American Medical Association, the American Public Health Association, the Association of Health and Territorial Health Officers, the United States Public Health Service, the Vaccine Advisory Committee of the National Foundation for Infantile Paralysis, and special consultants who, for a number of years, have been particularly interested in this matter of provocation.

At the meeting in New York on the 18th—and the complete statement was published in the New York Times, Sunday morning, the 19th, and anyone who wishes to see the complete statement can get the Times and read it; and I will, for the record place it here and it can be used—the group unanimously decided upon certain statements that would be used as guides to physicians and health officers in advising their patients and the public.

Now these are not laws and rules that must be followed but these are statements to help the physicians and the health officer, to guide the physician and health officer in advising the patients and the public about this matter of provocation.

Now, we all admit that there is a slight risk if a person is infected with poliomyelitis and receives whooping cough vaccine. We all admit that there is a slight risk in having a paralysis in the arm that receives the injection; no one questions that slight risk.

In large epidemics, and I can only speak of one because it was in Sioux City in 1953, and that was the city in which the gamma globulin test was carried out and the attack rate in that epidemic is one of the heaviest attack rates ever reported in the United States. It was somewhere between 300 and 400 per hundred thousand. That is a terrific attack rate.

In that city a certain number of children received gamma globulin and a similar number of children received dummy shots made of gelatin. there has been a great deal of contention about whether the dummy shots caused a few cases of paralysis as opposed to the population that didn't get inoculated. Now, remember, this is a terriffic attack rate. Certainly all of us will agree that the risk to those who received the gelatin was not great; if there was any provocation at all it was not a great risk.

Now, everybody agrees on that because you can look at the figures. Some people will even argue as to whether there was any provocation. I don't think that that is necessary. It is not necessary to carry it to that point.

Now, gelatin didn't protect these children.

Now, let us turn to the question of whether we will give during the summer months when there is poliomyelitis around, a substance that has protective qualities to your population, or whether you won't. Will you refuse to give this protective substance because there is a slight risk and the risk is small?

Let us examine this, and I now read this, which is a statement, by the way verbatim, that was given in New York. Let us turn to what evidence we have regarding the vaccine and its provoking effects. If you will permit me I will read it:

In Southern States in 1954, at the time of the field trial of poliomyelitis vaccine, cases of poliomyelitis were already occurring undoubtedly with associated symptomatic infections without evidence of provoking effect of the vaccine.

In 1955 in 14 Southern States during the 8-week period following April 16, some 2,300,000 injections with the Salk vaccine did not show evidence of a significant provoking effect. It must be emphasized that when poliomyelitis vaccine is given to large numbers of individuals during epidemic periods, a small proportion receiving the vaccine will subsequently experience paralytic disease. This is because the vaccine is not 100 percent effective.

Individuals receiving it during the early silent period of an infection may not be protected, but may be subject to a localizing effect of paralysis at the site of injection, and a certain number of cases erroneously reported as poliomyelitis will actually be instances of other diseases with clinical similarities.

It should also be emphasized that the small risk of the provoking effect of injections can be probably reduced still further by the avoidance of any such injections in individuals while they are exhibiting symptoms of minor illness, especially fever, sore throat, or gastro-intestinal upsets.

This following statement is extremely important, and I think it should be driven home to every physician, and every health officer:

The vaccine moreover should not be given to individuals in a household where a case of poliomyelitis has just occurred, since almost all of the other members of the household are already infected when the case is identified. Such an infection at this time may provoke paralysis.

In summary, those present at the meeting agree that the total preventive effect of the vaccine in a period of rising poliomyelitis incidence should be much greater than the possible hazard from the provoking effect of the injection. Therefore, the slight hazard of provocation is insufficient to limit the injection of poliomyelitis vaccine even in the presence of a rising incidence of poliomyelitis in the community.

Dr. PAUL. Is there any discussion on Dr. Rivers' statement?

Mr. SPRINGER. I would like to ask this, Dr. Rivers: May I say that I am in agreement with what you have said and there is just this one thing: Are we likely to receive any situation which would result adversely to the entire program as a result of cases of incidence occurring which would result in something similar to the Cutter case?

Dr. RIVERS. I don't think so, sir, for the simple reason that this did not happen in Sioux City or in Houston, Tex., or in Provo, Utah, with a gamma globulin situation, where we used the dummy shots. So far as I know there was nothing of this kind occurring last summer when we used the vaccine, and a certain number of the children did come down within the first month of the time they received the vaccine.

The placebo group showed that there were just as many in the placebo group as there was in the vaccinated group so the two groups are very much alike. They were not coming down because of provocation or because of a bad vaccine. Yet, so far as I know, and Dr. Francis can answer this better perhaps than I can, so far as I know there was no criticism because of these children coming down within a month after they had been vaccinated. The public fairly well knows that you

can't expect an effect under a month in preventing paralysis. I think Dr. Francis can answer that better, probably, than I can.

Dr. FRANCIS. We were very anxious a year ago to gain any information we could along these lines, and we alerted the health officers and the physicians of all of the communities to be particularly careful in reporting and in the investigation of any cases which do occur in this period. In fact, we had asked to be notified by telephone or as rapidly as possible of any instance that appeared to have any possible correlation to vaccine.

When the data were tabulated, as Dr. Rivers has said, the incidence in the vaccinated and those receiving the placebo was the same. In fact, during this period, up to 4 weeks after the third injection, the rates were 2.4 per 100,000 in those receiving vaccines, and 2.4 in those receiving placebo, and 3 in those that were not inoculated. So here I think we had evidence that there was not provocation from the vaccine or from the placebo.

In the observed areas, and since these involved many more of the Southern States, the same situation held, and at that time there were 103 cases that developed during the period in the observed areas, and 48 of those in the State of Texas. The rates in the vaccinated were 4.7, and in those specifically designated as controls it was 5.1, and you will recall these controls were not inoculated; and in the others, that is, the ones that said no, the rate was 3.2. So here again there was no evidence.

If one views them chronologically or in any other way that we are aware of, there was no evidence that at one time or another there was any real difference between them. So we concluded on that basis that there was no evidence of exaggerated instance that could be related to inoculation.

Secondly, we did not find any suggestions of localization related to the site of inoculation.

Thirdly, we had in this entire period, I think in the vaccinated population of the placebo area, 1 case occurring in a household associate of an inoculated person, and 1 in the observed areas, and an equal number or so in the controls. So that there was again no evidence of transmission from inoculated children.

Mr. SPRINGER. Dr. Rivers, would you develop, just in a few sentences there, the reasons again for not vaccinating the members of a family?

Dr. RIVERS. This is a very interesting situation and Dr. John Paul and others have worked out the situation and clarified it.

When a child in a family, or when a diagnosis of poliomyelitis has been made on a child in a family, that is when the diagnosis is made, and you don't usually do anything until the diagnosis is made—but when the diagnosis is made, 80 percent of the other household members at that particular time are infected, and they may have virus in the blood and would be just ripe for a provocation if one would occur.

Now, Dr. Paul, I think, will say that of the nonimmune people in the family—and I said 80 percent of the household, and that includes the immune and not immunes, too—I think Dr. Paul would say that pretty near 100 percent of the nonimmune children or the nonimmune members of the family at that time would be infected and might have virus in the blood: and so there is a group that we can put our finger on and say that this is a group that should not be vaccinated at this

time, but wait and do it later. I think Dr. Paul would agree with me on that.

Mr. SPRINGER. Why does the administration of the vaccine accelerate it?

Dr. RIVERS. It doesn't have to be the vaccine. An injection of salt solution would do it. Just the mere insertion of a dry needle, a dry, sterile needle into the muscle will do it. Actually, it doesn't have to be the vaccine. This situation of provocation was first noticed not with poliomyelitis vaccine, but was noticed with other injections; and injections of novocaine will do it; injections of penicillin will do it, and as a matter of fact penicillin is one of the bad offenders. The cruder the material and the more irritating the material that is injected, the more likely is provocation to take place.

It just so happens that our polio vaccine is, in spite of what the chemists say, a pretty nice looking substance, and it is nonirritating; it consists of a balanced salt solution and minimum amounts and just traces of protein-treated formalin, and the materials are not irritating near so much as some of the other substances.

Now, you don't have to limit this to injections. Trauma: for years it has been advised that children shouldn't have their tonsils removed during the summer because it seems to lead to paralysis or may if the person is infected, paralysis which is bulbar type, the very severe and fatal type. Operations of any kind where you have to have trauma of the muscles—if it is an elective operation on a child, and there is a severe epidemic, it has been advised to not undergo these traumas during this time. So it is not only an injection.

Now, if you ask me just the mechanism of provocation, no one can answer that at the moment. There are many theories, but there is absolutely no one can make his theory stand up against the others at the moment.

The. CHAIRMAN. Are there further questions? Dr. Paul?

Dr. PAUL. Dr. Rivers used the word "trauma." That is spelled t-r-a-u-m-a, and it means injury. Before going to the last item I want to make it very clear that we want all of those on the panel who would like to discuss any of these matters further to please do so.

Dr. SABIN. I would like to ask a question that I promised Dr. Rivers I would ask him. He has made himself very clear on the point of rising incidence when there is very little poliomyelitis in the community and he has made himself very clear on the household in which there is a great deal of potential infection. It is also known from Dr. Salk's experiments on monkeys that despite the purity of this vaccine that when it is given on the day or the day after inoculation of virus in monkeys, it can give rise to a higher incidence of paralysis than it controls.

I wonder if Dr. Rivers would like to comment on the space in between, the rising incidence, and the infected home, the severe epidemics of short duration, and long duration, and health officers and physicians are going to face those problems, too. I wonder if he has some thoughts on that.

Dr. RIVERS. I think this becomes a personal matter where every man has a right to his own opinion. The statement I made previously as an opinion was that I think probably 99 percent of the people will agree to it.

Now, Dr. Sabin is getting into an area where there will be a certain amount of discussion. Certainly epidemics of poliomyelitis are not as short lived as Dr. Sabin might indicate. Epidemics of influenza are very short lived, and epidemics of poliomyelitis are like this.

Certainly, on the upstroke of an epidemic, and that is what I meant when I said by a rising incidence, and that is what is meant on that statement; but on the upstroke of en epidemic you can go in soon enough so that the slight amount of damage that you might do to a few people will be so greatly outweighted by the good that you will do to the mass that you don't hesitate to go in. You have got plenty of time at that time to have your vaccine do some protection.

Personally, if I knew that I was on the downgrade of an epidemic and it would be over within a month, I do not think that I would give the vaccine at that time. It takes a month to get enough protection to really show up like we would like to have it do, and you might cause some damage at that time. I would hesitate perhaps on the downstroke of the epidemic to give it.

In prolonged epidemics I certainly would give it. As an example, there is such an epidemic in progress in Puerto Rico now, that has been going on for several months, and it looks as though it is going to go on for several months longer. How long no one knows. I would certainly go in, if I had the vaccine, and I could do it, I would go in to Puerto Rico and vaccinate. I would have gone in there a month ago and would have vaccinated if it had been possible.

The evidence that there is a great deal of damage done by provocation during severe outbreaks, what evidence we have, and it is the best evidence, is Sioux City, Iowa, in 1953. As I said, that is the most severe epidemic that we know about. The rate was terribly high, and injections were given, gelatin injections, and no great damage was done.

There are certain people and people who have worked on this who would say the higher the attack rate in an epidemic, the more good you are likely to do because you protect more people, realizing that perhaps the hazard is a little bit higher in that instance, too: but the good that you do is also higher.

Now, there is a difference of opinion on this. I have stated what I would do, and certainly on the upswing of an epidemic I would give it and on the downswing if I thought it was going to be over in a month I wouldn't give it; and in a prolonged epidemic I would. There will be differences of opinion, and I think those differences should be respected.

That is, after all, the parents of the patient we give the facts to is the one who ultimately makes the decision. I don't think any doctor or any health officer would even attempt to force this on anybody. I think if I give them the facts, you can let them decide.

Dr. MAYER. I would like to make a statement for the record, in view of the remarks just made by Dr. Rivers, and the remarks before.

I agree entirely with respect to the impurities, that the amounts are very small. As you ordinarily think of quantities of material, these are very tiny amounts. But I think that it should be clear that even these small amounts can, in some situations, be potentially dangerous, and I want to be on record with the recommendation that every effort should be made as soon as possible to remove these impurities.

As was stated yesterday, there is approximately 1,000 parts of impurity for one part of virus in the present product, and if we purity we get rid of penicillin to which some people feel there is objection, and we get rid of streptomycin and the kidney material, and we can improve the safety testing, and we can get a real margin of safety rather than an assumed one, and we can adjust the dose of vaccine to that quantity we feel is necessary.

Mr. ROBERTS. What are some of the dangers that might result from these impurities?

Dr. MAYER. There are some indications, and I say only indications, from very limited experiments in animals, that kidney damage can result. There are experimental workers who have failed to confirm this work, and my own opinion is that the difficulty in this area lies in the fact that when you do an experiment with 10 or 20 or even 50 animals, it may be very difficult to pick up this effect.

But what some of us are worried about is that the injection of the kidney material, and to some extent this is also true for the penicillin and possibly streptomycin, that the injection of this material repeatedly over a period of years, into a very large number of individuals, may result in disease in a small fraction of these individuals. We do not know, and we have no way of knowing whether this will be 1 in 10,000, 1 in 100,000, but there are some of us who believe that this possibly has to be recognized.

It would be very difficult, I believe, to determine experimentally whether this danger is real or is not real. It would take an enormous study, I believe. I think it would be much easier to remove this offending material rather than to make such a study.

Mr. ROBERTS. I believe you said before that it is your firm opinion that these impurities can be removed by processes now known to chemists?

Dr. MAYER. Yes, sir.

Dr. PAUL. We come now, Mr. Chairman, to an attempt to summarize to some extent my own personal opinion of the conference and I think it will be very brief.

I think the conference has spoken for itself, and rather than try to reiterate many of the features that have been reviewed here at some length, I will only mention 1 or 2 points.

I think it is important for us to indicate those points on which the panel seem to be in substantial agreement. As we said, at the introduction we expected there to be some slight differences and I am very glad that there have been. It would have been most unfortunate if we had been a dogmatic group with fixed answers all in one direction.

Now, to turn back to certain points in the agenda on which we have expressed agreement, I think Dr. Sabin's primary discussion of what the problem of poliomyelitis is in this country has been an important one to refer back to. He has pointed out that over the years we have a rising an an increasing incidence of this disease far greater than it was in our grandparent's time and now we have around an average of thirty-some-thousand cases a year and sometimes it has been over 40,000.

I mention this only because it is in this country, the United States, and there are certain other countries, the Scandinavian countries, if I may mention 1 or 2, who have the greatest poliomyelitis problem. It

is quite different from the problems in the rest of the world, as Dr. Sabin intimated. This is a situation which really cries out for some kind of control, of which immunization seems to be a logical approach.

Obviously, there is everyone here in this group who hopes that immunization is going to be done properly.

Now, I will not try to review the story of the development of the Salk vaccine and we have heard also of the accidents which have happened. Some lots produced by two companies, and just exactly what has been the cause is not clear, but it has meant an immense amount of concern to all of the people involved, and there has been a vigorous review of the situation and a revamping of the efforts to make the situation better. I will not try to reveiw them, but I think I can speak for the panel, that they have been unanimous in their belief that if a better vaccine can be made every effort should be made to make it.

What all of those improvements may be, Dr. Mayer has emphasized his views and Dr. Shannon has pointed out his views and Dr. Sabin has intiated the problem of putting in attenuated strains if and when they have been proven to have antigenic capacities. Those things, I feel, is the spirit of this panel, but we took a vote on one of them this morning, and the report was practically unanimous.

Now, of course, comes the problem of when these improvements come to pass. I woudn't try to predict what that would be. But the mention of 6 months has been made, and others have said it will take much longer. That, of course, has some bearing on the problem that was discussed as to whether or not the present program should be interrupted until new and better vaccine material would be available.

I think we have heard that discussion at some length and it is not an easy point to settle, and all I can do is point out that this was carefully considered and the vote of that situation in regards terminating the project was 8 to 3 in favor that it should not be terminated out of 11 people voting. That did not represent the entire panel.

Now, I do not want to pursue the other important matters. We have heard many things about them. I just want to end with one particular note, and that is that as Dr. Sabin pointed out in his discussion yesterday, a great advance in the control of poliomyelitis is in the making and in fact seems to have been made. How to do it without difficulties, and without trouble, problems of its implementation have not all been settled. But I think that these minor differences might almost be considered trivial matters in the light of the possibility of controlling this disease which is in sight.

The CHAIRMAN. Thank you. Once again I want to thank you and this panel.

May I say, in connection with your last statement, I believe with such men as we have had sitting before us here for the past 2 days, all conscientiously working on the problems that grow out of any vaccine, or any mass inoculation program, I have confidence that those problems will be solved and will be solved perhaps earlier than some of us believe. I have so much faith in all of you.

I told Dr. Sabin, I believe yesterday, that I am not a scientist except in spirit, and I told him at that same time that I always thought the world lost a great bacteriologist because I had to give up some pursuit of that subject at an earlier age. I have had an intense interest in

science all of my life. I do not know a great deal about it, but I have received, I think, a fairly liberal education on some of the important questions that I and this committee have to face as a result of appearance here of this fine panel and the manner in which it has been conducted.

You gentlemen may not be aware of it, members of the committee certainly will be, that many of the questions you have answered for us and that are now part of the record, giving your opinions on whether that is the final answer or not, they will be asked of us when and if we take a piece of legislation to the floor. Any one of us arising in the well of the House to explain a bill, realizes that the Members are not going to be as much interested in the language of the bill as they are in questions which have been discussed by this panel and very ably discussed.

So as we bring it to a close, I just want you to know how very deeply the committee appreciates what you have done and the help rendered by the Academy of Science in assembling this panel.

The committee will stand adjourned.

(Whereupon, the committee adjourned.)

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